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COLLECTED PAPERS
of
THE MAYO CLINIC

ROCHESTER, MINNESOTA

EDITED BY
MRS. M. H. MELLISH

VOLUME VII

1915



PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY

1916

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FOREWORD

IN order that the Collected Papers each year may contain an approximately uniform amount of material, it has been necessary to omit from the present volume a number of articles that were read before societies but not published during 1915. Some of these papers are parts of series of studies already published, and will be included among the Papers of 1916. Those not belonging to consecutive series have been abstracted in this volume.

MRS. MAUD H. MELLISH

Editor

ROCHESTER, MINNESOTA

June, 1916

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CONTENTS

ALIMENTARY CANAL

	PAGE
TUBERCULOSIS OF THE TONGUE.....	3
INFECTIONS OF THE MOUTH.....	19
THE RELATION OF AMEBIASIS TO PYORRHEA ALVEOLARIS.....	25
BILATERAL PAROTID TUMORS.....	37
STUDIES IN SURGERY OF THE TONSIL.....	52
II. Tonsillectomy.....	52
THE BACTERIOLOGY OF ULCER OF THE STOMACH AND DUODENUM IN MAN.....	58
THE TROPHIC ELEMENT IN THE ORIGIN OF GASTRIC ULCER.....	70
A STUDY OF THE GASTRIC ULCERS FOLLOWING REMOVAL OF THE ADRENALS....	87
THE ROENTGENOLOGIC DETERMINATION OF GASTRIC MOTILITY.....	96
ROENTGEN DIAGNOSIS OF GASTRIC CANCER, WITH SOME ILLUSTRATIVE CASES	123
GASTROJEJUNAL ULCERS—THEIR ROENTGENOLOGIC AND SURGICAL ASPECTS..	156
THE ESSENTIAL FACTORS IN THE DIAGNOSIS OF CHRONIC GASTRIC AND DUODENAL ULCERS.....	174
NOTES ON GASTRIC AND DUODENAL ULCERS.....	184
THE DIFFERENTIAL DIAGNOSIS OF LESIONS OF THE STOMACH AND DUODENUM	194
GASTRIC ULCER.....	204
FOREIGN BODIES SWALLOWED BY AN INSANE WOMAN.....	218
THE ROENTGENOLOGIC DIAGNOSIS OF DUODENAL ULCER.....	220
CHRONIC DUODENAL ULCER.....	234
ROENTGEN OBSERVATION OF THE GALL-BLADDER AND HEPATIC DUCTS AFTER	
PERFORATION INTO THE DUODENUM.....	247
PAPILLOMAS OF THE GALL-BLADDER.....	249
CHOLECYSTOSTOMY VERSUS CHOLECYSTECTOMY.....	256
RESTORATION OF THE BILE-PASSAGE AFTER SERIOUS INJURY TO THE COMMON	
OR HEPATIC DUCTS.....	264
PATHOGENESIS OF SPONTANEOUS AND EXPERIMENTAL APPENDICITIS, ULCER OF	
THE STOMACH, AND CHOLECYSTITIS.....	276
AN EPIDEMIC OF APPENDICITIS AND PAROTITIS, PROBABLY DUE TO STREPTOCOCCI CONTAINED IN DAIRY PRODUCTS.....	282

	PAGE
ACUTE PERFORATIONS IN ABDOMEN—TRAUMATIC, SPONTANEOUS.....	292
SUBDIAPHRAGMATIC ABSCESS.....	298

UROGENITAL ORGANS

PERINEPHRITIC ABSCESSES.....	311
SIGNIFICANCE OF VESICAL SYMPTOMS IN THE DIAGNOSIS OF RENAL CONDITIONS	320
STONES IN THE URETER.....	327
CLINICAL REVIEW OF 240 CASES OF NON-SURGICAL INFECTION OF THE KIDNEYS AND URETERS.....	336
ANURIA FOR FIVE AND ONE-HALF DAYS IN A PATIENT ON WHOM LEFT NEPHREC- TOMY HAD BEEN DONE.....	346
PROCEDURES FOLLOWING NEPHRECTOMY.....	349
I. The Transperitoneal Closure of Duodenal Fistulas Following Neph- rectomy.....	349
II. The Two-forceps Method for the Ligation of Vascular Pedicles, with Special Reference to Nephrectomy.....	355
III. The Management of the Ureter after Nephrectomy for Tuberculosis	361
FOREIGN BODIES IN THE URINARY BLADDER.....	364
REPAIR OF SMALL VESICOVAGINAL FISTULE.....	373
THE TREATMENT BY HEAT OF ADVANCED CANCER OF THE CERVIX (PERCY'S METHOD).....	378
THE RELATIVE MERITS OF THE OPERATIONS FOR CANCER OF THE UTERUS...	385

DUCTLESS GLANDS

THE ISOLATION IN CRYSTALLINE FORM OF THE COMPOUND CONTAINING IODIN WHICH OCCURS IN THE THYROID; ITS CHEMICAL NATURE AND PHYSIO- LOGIC ACTIVITY.....	393
THE RELATIONSHIP OF THE PATHOLOGIC HISTOLOGY AND THE IODIN COM- POUNDS OF THE HUMAN THYROID.....	422
PATHOLOGIC CHANGES IN THE MUSCULAR AND NERVOUS SYSTEMS IN GOITER..	438
STUDIES IN BLOOD-PRESSURE.....	448
I. Blood-pressure and Thyrotoxicosis.....	448
GOITER AND LIFE EXPECTANCY.....	456
RESULTS OF OPERATIONS FOR EXOPHTHALMIC GOITER.....	463
MEDICAL TREATMENT OF DIABETICS PREPARATORY TO SURGICAL TREATMENT	476
THE RELATION OF THE ADRENALS TO THE PANCREAS.....	485

	PAGE
STUDIES IN THE PATHOLOGY OF THE SPLEEN.....	500
II. Pathology of Spleens Removed for Certain Abnormal Conditions of the Blood.....	500
DISEASES OF THE SPLEEN.....	511
III. Clinical Notes on Splenectomy.....	511
IV. Splenectomy for Splenic Anemia in Childhood and for Splenic Anemia of Infancy.....	517
THE RELATION OF THE SPLEEN TO CERTAIN ANEMIAS.....	529
SURGICAL CONSIDERATIONS OF SPLENECTOMY.....	541

HEAD, TRUNK, AND EXTREMITIES

HYDROCEPHALUS, SPINA BIFIDA, AND ALLIED DISEASES.....	551
CIRROID ANEURYSM.....	561
EVISCEATION AND ITS SUPPOSED RELATION TO SYMPATHETIC OPHTHALMIA..	573
CORRECTION OF DEPRESSED FRACTURES OF THE NOSE BY TRANSPLANT OF CARTILAGE.....	579
ANTRUM TROCAR AND IRRIGATING CANNULA.....	585
FIBROLIPOMA OF THE LARYNX.....	587
THE NOSE AND THROAT IN THE ETIOLOGY OF GENERAL DISEASES.....	593
RADIOGRAPHIC DIAGNOSIS OF METASTATIC PULMONARY MALIGNANCY: A RE- PORT OF 71 POSITIVE CASES.....	606
THE TREATMENT OF CHRONIC NON-TUBERCULOUS EMPYEMA.....	618
NON-STRANGULATED DIAPHRAGMATIC HERNIA DUE TO INDIRECT INJURY....	645
DESMOID TUMORS: REPORT OF TWO CASES IN WHICH THE TUMOR OCCURRED IN THE OPERATIVE SCARS.....	655
VARICOSE VEINS.....	660
THE TRANSPLANTATION OF BONE IN UNUNITED FRACTURES OF THE SHAFT OF THE HUMERUS.....	669
SOME MECHANICAL DERANGEMENTS OF THE KNEE-JOINT.....	681
TRANSPLANTATION OF BONE FOR NON-REGENERATION OF THE TIBIAL SHAFT..	701
OPERATIVE TREATMENT OF BUNIONS BY THE MAYO METHOD.....	705

TECHNIC

INTRATRACHEAL ETHER ANESTHESIA: A NEW APPARATUS AND INTRATRACHEAL TUBE.....	715
STAINING SECTIONS OF LIVING TISSUE, UNFIXED.....	722
A DEVICE FOR HOLDING SOLUTION BOTTLES IN OPERATING ROOMS.....	731
A SIMPLE OPERATING MALLET.....	733
DESCRIPTION OF A SELF-RETAINING BLADDER RETRACTOR.....	734

GENERAL PAPERS

	PAGE
SHOCK AND HEMORRHAGE: AN EXPERIMENTAL STUDY.....	739
ELECTIVE LOCALIZATION OF STREPTOCOCCI.....	764
THE ETIOLOGY AND EXPERIMENTAL PRODUCTION OF HERPES ZOSTER.....	779
VISCERAL CRISES IN ANGIONEUROTIC EDEMA.....	823
OBSERVATIONS ON THE CLINICAL PROGNOSIS OF SYPHILIS.....	836
CLINICAL OBSERVATIONS ON LUEPIC DISEASE OF THE HEART AND AORTA.....	846
SNUFF-POISONING.....	854
THE EXAMINATION, PREPARATION, AND CARE OF SURGICAL PATIENTS.....	859
ERRORS IN ANATOMIC DEVELOPMENT: THEIR CAUSE AND SURGICAL SIGNIFI- CANCE.....	865
INFECTION A CAUSE OF LOCAL AND GENERAL DISEASE.....	879
STUDIES IN THE ETIOLOGY OF CANCER.....	885
VI. Facts Versus Speculation in the Professional Conception of Cancer..	885
VII. A New Classification of Neoplasms.....	898
VIII. The Evolution of Cancer.....	903
IX. The Relation Between Chronic Mastitis and Carcinoma of the Breast	918
X. Melanoepithelioma.....	923
THE NECROPSY AS A PUBLIC SERVICE.....	937
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INDEX OF CONTRIBUTORS.....	947
BIBLIOGRAPHIC INDEX.....	953
INDEX OF SUBJECTS.....	961

ALIMENTARY CANAL



TUBERCULOSIS OF THE TONGUE*

LUIGI DURANTE

As deduced from autopsy reports and clinical records, tuberculosis of the tongue is infrequent. Willigk,¹ in 1317 necropsies of tuberculous subjects, found tuberculous lesions in the tongue twice only; Fowler,² in 382 autopsies, found it 4 times; Fischer,³ 3 times in 1500; Chiari,⁴ 12 times in 625; and Adami,⁵ in 417 autopsies of tuberculous cases, found none.

In statistics on pulmonary tuberculous lesions in German sanatoria Hamel⁶ records one case of tuberculosis of the tongue in 12,369 subjects. Von Ruck⁷ gives the frequency of 0.38 per cent. in tuberculous subjects deduced from a material of 5000 patients studied in Winyah Sanatorium.

Literature covering the contributions to the casuistics collected by Dalla Vedova⁸ previous to 1906, and by me from January 1, 1901, to October 20, 1915, comprises about 250 cases of primary and secondary tuberculosis of the tongue, some of which are recorded without anatomicoclinical details. Blancard's⁹ article reporting three interesting cases is the latest contribution.

The reason of the relative infrequency of tuberculous lesions of the tongue, an organ so near the source of infection, is probably due to two factors: (1) To the particular structure of the lingual mucosa which resists the direct penetration of the *Bacillus tuberculosis*; and (2) to the natural resistance which all striated muscles present to the lodgment of the bacilli. This resistance has been attributed by certain writers to antibacterial and antitoxic action, accentuated or reinforced by glycogen. It acts against micro-

* Submitted for publication October 28, 1915. Reprinted from the *Annals of Surgery*, 1916, lxxiii, 143-154.

organisms in general and against the *Bacillus tuberculosis* in particular, as was demonstrated *in vitro* by Teissier.¹⁰ It has also been ascribed to the continuous fibrillation which obstructs the attack of the bacilli. Nevertheless, though the facts are indisputable, its fundamental reason remains obscure.

The larger proportion of these cases occur between the twentieth and fiftieth year; rarely above the latter age, though the case reported by Zintsmaster¹¹ was in the eightieth year. One case, that of Reimann,¹² occurred at nineteen years. None are recorded as having occurred in infancy, the age in which tuberculous lesions are so frequent and wide-spread.

These considerations seem to justify the deduction that the tuberculous process in the tongue is assisted by the causes common to middle age, such as trauma of the mucosa by the stem of a pipe, by carious teeth, by toxic glossitis, etc., and these causes, more frequent among men, explain the greater frequency of tuberculosis of the tongue among men. Chvostek's¹³ statistics show 1 woman to every 4 men; Schliferowitsch's¹⁴ show 1 in 5; Delavan's¹⁵ show 1 in 23.

The routes by which tuberculosis localizes itself in the tongue, though theoretic, are reducible to certain organs: (1) By the blood-vessels; (2) by the lymphatics; (3) by direct infection, and (4) by extension. Practically these routes cannot always be determined and the frequency of infection by a given route can be determined with scientific precision only with difficulty. Also, in cases in which the lesion of the tongue represents the late secondary localization of a primary bronchopulmonary tuberculous process it is always dubious to affirm or exclude by which of these routes, whether by the blood-vessels, the lymphatics, or by direct inoculation by way of the excretion, the bacilli have reached the lingual focus. All three routes are possible, but no one character of the clinical course or of the microscopic findings permits a sure differentiation. The fourth route, which I have stated as theoretically possible, that of the extension to the tongue by continuity of a tuberculous process in a neighboring region, I have not found recorded in the literature.

The tongue is one of the first organs which can come into contact with the infectious elements by way of the air or by the passage of food, and by reason of the diminished vitality of the integument in circumscribed areas, determined by the many traumatic causes mentioned, can become primarily the seat of a tuberculous lesion. The theoretic possibility of a primary tuberculosis of the tongue is practically confirmed by two cases described by Clarke¹⁶ and by Schliferowitsch.¹⁴ These were operated on for tuberculous ulcers of the tongue and died from other causes. Tuberculous lesions were not found in other organs. Literature records¹⁷ many other cases of "primary" tuberculosis of the tongue, but this term should be accepted in a clinical sense only, since the cases were not controlled by autopsy.

In the majority of cases tuberculosis of the tongue has a localization secondary to a tuberculous process in other parts of the organism, *e. g.*, in the anus (Burquoy¹⁸) and in the epididymis (Weber¹⁹).

The anatomic forms which tuberculosis of the tongue may assume do not represent a distinct anatomic entity, but often diverse forms of the same evolutionary process or varying anatomic aspects from case to case, and from region to region, according to the virulence of the bacilli and the reaction and local resistance of the tissues. For this reason they have a clinical rather than an anatomic interest. Whatever may be the final anatomicoclinical form of tuberculosis of the tongue, the beginning is always characterized by specific connective tissue, new formation of tuberculous nodules, which may be localized separately in the dermis of the mucosa or in the lingual parenchyma.

From this distinct initial localization of the tuberculous process may originate two clinically different types. The first, namely, the connective tuberculous new formation, if in the lingual dermis, assumes characteristics approximating cutaneous lupus. It presents itself initially as a plaque of gray color somewhat elevated above the surrounding mucosa without inflammatory reactions, and hard to the touch. It is formed by the grouping of small miliary nodules which, if they preserve the sclerotic form, are

spoken of as glossodermatitis tuberculofibrosa. Should these ulcerate, they are called glossodermatitis tuberculo-ulcerosa. These two distinct forms of lingual lupus through the possible transition to another, sometimes assume aspects with difficulty referable to a fixed type. The lupous lesions of the tongue are always accompanied by lupous lesions of the buccal mucosa, of the nose, or of the skin of the face, and represent a complication not relatively rare. Licht Institute reported over 2000 patients affected by lupus vulgaris of the face in whom lingual lupus was noted only 15 times.

When, on the other hand, the tuberculous elements affect primarily the parenchyma of the tongue (or rather the intramuscular connective tissues of the tongue, since the question arises whether a true primary tuberculous myositis ever exists), they may coalesce in such a way as to constitute a single nodule,—nodular tuberculosis, confluent tuberculosis, granuloma tuberculare,—or, if they may be disseminated in various regions—disseminated miliary tuberculosis, tuberculosis nodulare, multiple or gummatous.

Each form, though the confluent more readily than the disseminated, may maintain its anatomic individuality for months and years, and simulate a neoplastic lesion or the localization of tertiary lues. It tends in the early stage to caseous necrosis, becoming fluctuating (cold abscess of the tongue) and opening to the surface with the formation of a large ulcer or a fistulous opening. The typical tuberculous ulcer has irregular margins, sinuous, soft, and reddened, with a soft yellow base. It is surrounded by easily bleeding granulations. It may appear in any region of the tongue, but with more frequency on the margins and tip. The adenitis which accompanies it is often bilateral and slightly painful to pressure.

From a review of the clinical history one deduces that the persistence of the two clinical individualities, the nodular form and the ulcerative form, is influenced by the condition and the course which the tuberculous infection assumes in other parts of the body of which the lingual lesion is generally a secondary localization.

The form which for most of the time maintains the nodular type, single or multiple, accompanies a tuberculous infection, generally of the lung, with a slow course, not destructive, or is an indirect primary form. The forms which tend rapidly to caseous necrosis are habitually concomitant with and secondary to deep and destructive lesions of other organs.

Literature records still another form of tuberculosis of the tongue, of a verrucose (François-Dainville²⁰) or papillomatous type (Danlos and Levy-Frankel²¹), so called from the aspect which the mucosa may assume when its papillæ become infiltrated by a tuberculous granuloma of the lymphoid type. There has never been described in the tongue the type of inflammatory hypertrophic tuberculosis of a pseudoneoplastic character found in the smooth musculature of the pylorus, of the cecum, and in striated muscles.

The result of the search for the bacillus of Koch in tuberculous glossitis is usually positive; though sometimes in cases of undoubted tuberculosis of the tongue it may be negative (Dalla Vedova,⁸ Campbell,²² Trimble,¹⁷ Schliferowitsch¹⁴). In order to exclude the presence of the specific bacteria in the affected tissues it is necessary to supplement the biologic test by the use of both Ziehl-Neelson's and Gram's methods of staining. We know, in fact, following the works of Mircoli,²³ Much,²⁴ Constantini,²⁵ etc., that contemporaneously with the morphologic variability of the *Bacillus tuberculosis* its chemical properties and staining reactions vary also. There exists, indeed, a species of *Bacillus tuberculosis* of the typical form of rod which does not stain by Ziehl's method but does stain by the prolonged method of Gram; and a granular form which has a chromatin affinity exclusively for the Gram stain.

The symptoms of lingual tuberculosis vary following the anatomic form which it assumes and following its stage of evolution. The characteristics of tuberculous infection in all the organs, the absence of subjective disturbance in the initial stage of the lesion, marks the beginning of tuberculosis of the tongue which develops slowly and almost painlessly until it assumes the ulcerative form. At this stage there is an abundant salivation (ptyalism) from the specific reflex secretory stimuli pertaining to

the ulcerated surface and mild spontaneous tenderness through the diffusion of the inflammatory process to the lymphatic sheaths of the nerve filaments and through the pain due to the passage of food. Such pain, together with the inflammatory condition, often limits the normal mobility of the tongue on account of the facility with which it is complicated by secondary infection, accompanied early by a somewhat painful regional adenopathy. This adenopathy in general is absent in the closed, non-ulcerative form of lingual tuberculosis.

Diagnosis.—The diagnosis in the initial stage of the process of evolution presents generally great difficulty when the attempt at diagnosis is limited to the direct physical findings. A review of the literature in this connection impresses one with the frequency with which tuberculosis of the tongue is confused with epitheliomatous neoplasm or with tertiary lues. The first, most common, diagnostic error in this connection has often led to the amputation of the tongue and to the accompanying complementary operations of the neck, as in cases reported by Albert,²⁶ Hansemann,²⁷ Bull,²⁸ Dalla Vedova,⁸ Euteneurer.²⁹ The second diagnostic error leads to mercurial treatment, which has been actually employed in 180 reported cases.

Lupus of the tongue, in whatever aspect it presents itself, is not difficult to diagnose. It may be confused with the papillary or ulcerative lesions of lues; but the generic criteria which serve to differentiate the two lesions in any organ, anamnesia, the trial of specific serous methods of diagnosis, therapy, etc., or, better, the microscopic examination of the excised tissue, will serve to make the differentiation.

All the other forms of lingual tuberculosis present serious difficulties unless recourse be had to microscopic examination. The nodular form of intralingual tuberculosis, confluent or disseminated, in the beginning is quiet, without pain, not accompanied by a swelling of regional glands, and is simulated more frequently by the gummatous lesions of lues. To exclude the syphilitic affections, it should be noted that these have a predilection for the base of the tongue, while tuberculosis elects the tip; they are less painful

than tuberculous granulomas and in a few weeks ulcerate. Again, one should use the criteria mentioned above in the differentiation of the lupous form from syphilis of the tongue.

This nodular form of lingual tuberculosis may also be confused with actinomycosis, rarely with fibroma, lipoma, or sarcoma. Criteria of approximate differentiation can be found if we remember the characteristics noted as pertaining to each pathologic form. Sure criteria are difficult to find if we do not employ the direct examination of the tissue of the tumor.

The ulcerative form of lingual tuberculosis, especially if the lesion is primary and alone, assumes great surgical interest from its being easily confused with cancerous ulcer, because this is of much greater frequency than the first and because both have a predilection for the same age, the same sex, and the same lingual region. In typical forms the two ulcers can often be differentiated by a single direct examination; but often the tuberculous ulcer does not present the characteristics which I have recorded, but occurs with margins and with the base moderately indurated by inflammatory infiltration (Zintsmaster,¹¹ Dally,³⁰ etc.), spontaneously painful from the diffusion of the inflammatory process in the lymphatics and the nerve filaments. In such a case it is obvious how an error may easily take place because the differential characteristics, described for the two ulcers and for those omitted because they are intuitive, have substantially an academic value, not a practical one.

It is therefore not prudent that the diagnosis of ulcerous lesions of the tongue should be determined by a single method or by the clinical signs, but should be founded on an accurate histobiologic test. The removal of tissue for the histobiologic test and for the inoculation of guinea-pigs is the diagnostic means most certain and is the method of election to differentiate the neoplastic lesion of the tongue from tuberculosis. At least the histologic examination of the base of the ulcer in frozen sections during the operation should be done, thus sometimes preventing greatly destructive and useless intervention.

Prognosis.—The prognosis is favorable when the tuberculosis

of the tongue presents itself as a primary and unique lesion; less so when it is primary but has a multiple localization. It is generally unfavorable when the lingual lesion presents itself as a late localization and secondary as a bronchopulmonary process. In such cases it assumes the gravity which the tuberculous process has in the principal focus and does not follow the evolution.

Treatment.—The therapy of election, avoided by previous authors, has been operative when the tuberculous lesion of the tongue was single and circumscribed. In the multiple and diffuse lesions the treatment has been local with the common cautery. I have studied the following cases from the material in the Mayo Clinic:

HISTOLOGIC FINDINGS. SPECIMENS FIXED IN 10 PER CENT.
FORMALIN, BLOCKED IN PARAFFIN, SECTIONS STAINED WITH
WEIGERT-VAN GIESON AND UNNA PAPPENHEIM

CASE I.—The margin of the ulcer (involving the mucosa, the tunica propria, and in parts even the muscular stratum) shows extensive small-cell infiltration of the connective tissue, but no typical tuberculous nodules are present. In the lower strata (of the margin of the ulcer) a few muscle-fibers may be seen; these fibers have been split up into fragments by the small-cell infiltration, and are both degenerated and atrophic. The fundus of the ulcer, on the contrary, contains a great number of miliary foci, in which giant-cells may be seen; the latter are generally surrounded by lymphoid tissue, though a few epithelioid cells are found here and there. Caseous degeneration of these miliary tubercles appears to be extremely rare. The solitary tubercle as well as the larger tuberculous lesion, produced by the conglomeration of small nodules, is walled off by a dense zone of connective tissue. Extensive perivascular infiltration is found in every section.

Histologic Diagnosis.—Confluent ulcerating tuberculous granuloma.

CASE II.—The margins of the ulcer are composed of an intense small-cell infiltration, which has taken the place of all the original parenchyma. Here and there the infiltration is somewhat less dense, the cells are seen clustered together in groups, and on the periphery of these groups lymphoid cells are found breaking up

the muscular layer, the latter being atrophic and staining badly. In the lower strata, forming the fundus of the ulcer, numerous typical nodules appear; some of these, however, contain only lymphoid and epithelial cells. A few giant-cells are found scattered among the invading lymphoid tissue, although no attempt at tubercle formation could be traced. The blood-vessels show extensive perivascular infiltration.

Histologic Diagnosis.—Confluent ulcerating tuberculous granuloma.

CASE III.—The specimens removed at operation have not been preserved.

CASE IV.—Of the tuberculous nodule several blocks excised at different angles were examined: all contain the same histologic picture. Numerous miliary tubercles are found consisting of solitary nodules and of confluent groups of nodules separated by dense connective tissue containing very few nuclei, as in Fig. 1. The formation of individual nodules and the number of epithelial cells found in these nodules is characteristic of this particular type of tuberculosis of the tongue. In many of the nodules containing giant-cells of varied shapes and sizes, the nuclei being arranged peripherally or scattered throughout the cytoplasm, it is clearly shown that the giant-cell was formed by a gradual fusion of epithelial elements. The giant-cells appear to represent a form of syncytium due to the fusion of epithelial cells. In this case nodules containing lymphoid cells only are extremely rare. Bundles of muscle-fibers that have remained intact are few and far between. They present the picture of disintegration already described above. They appear to have been separated and pushed aside by the infiltrative process when the latter began to invade the connective tissue. As usual the blood-vessels show extensive perivascular infiltration.

Histologic Diagnosis.—Intraparenchymal tuberculous granuloma containing miliary nodules.

CASE V.—The margin of the ulcer, which involves the epithelium, the tunica propria, and, in part, the muscular layer, shows intense small-cell infiltration as well as typical, nodular tuberculous lesions. Fig. 3 represents a large sclerotic tubercle found on the edge of the ulcer at the periphery, of which numerous giant-cells of various shapes and sizes may be seen. The inflammatory infiltration extends as far as the intrapapillary connective

tissue in some places, invading the epithelium and paving the way for ulceration. The fundus of the ulcer also shows extensive small-cell infiltration and contains a great number of typical nodules in whose outer zone giant-cells are seen. A few muscle-fibers are found, both in the fundus and in the margin of the ulcer. These fibers are atrophic and stain badly. Extensive perivascular infiltration is seen around all the blood-vessels.

Histologic Diagnosis.—Intraparenchymal tuberculoma, containing confluent and ulcerating tubercles.

SUMMARY OF HISTOLOGIC FINDINGS

As may be readily seen from the description of the four cases mentioned above, the histologic picture found in tuberculosis of the tongue does not differ materially from that which is seen in the tuberculous lesions of other organs, especially of the striated muscles. Apart from the small-cell infiltration, which is not a typical feature in itself, the typical nodules characterizing tuberculous lesions may be observed in every case. In two out of three of our cases (presenting the ulcerating type of tuberculosis) these characteristic nodules could be observed only in the lower strata of the margin and in the fundus of the ulcer, a fact which suggests that in microscopic diagnoses both margin and fundus should be examined with special care. Three cases gave no data whatever concerning the actual histogenesis of the giant-cells. In the fourth, however, the formation of giant-cells as a direct result of syncytial fusion of epithelioid cells could be repeatedly demonstrated. The fact that extensive perivascular infiltration was found in every case seems to indicate that hematogenous infection plays a prominent part in the propagation of tuberculosis in the tongue.

SUMMARY OF CLINICAL OBSERVATIONS

Of the five cases of lingual tuberculosis I have described, two were women; in every case the age of the patient was between twenty and sixty. None of these came to autopsy. The question, whether any of these can be rightly described as "primary" tuberculosis of the tongue, must consequently be decided by the clinical

findings. In Cases I and IV no evidence of other tuberculous foci could be obtained by clinical means. In the three remaining cases the lesions of the tongue appeared to be tardy secondary manifestations of primary pulmonary tuberculosis.

In four cases (I, II, III, V) the lesions of the tongue had already assumed the ulcerating form at clinical examination; the ulceration was most marked at the edges, the granuloma itself being embedded deep down in the tissue.

In Cases II, III, and V the ulcer showed the typical characteris-

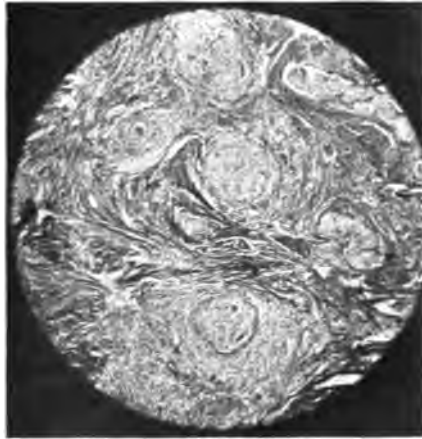


Fig. 1.—Case IV. Tuberculosis of the tongue; multiple tubercles forming a single nodule. Section stained with Weigert-van Gieson stain. Photomicrograph (80 diam.); showing four typical miliary tubercles forming one nodule, situated in the muscular stratum, surrounded by dense connective tissue.

tics of the disease, but in Case I both margins and fundus appeared hard and infiltrated and suggested an ulcerating epithelioma.

Case IV was of the nodular type and showed no change for ten years, at the end of which time the patient came for operation. The importance of the conditions under which tuberculous lesions develop, and the influence of these conditions on the progress of the disease and on the histologic picture which results, may be clearly seen in Case IV: The patient's personal history as well as the family history were entirely free from tuberculosis, the lesion

found in his tongue may be called primary inasmuch as no other foci could be discovered during clinical examination; the lesion

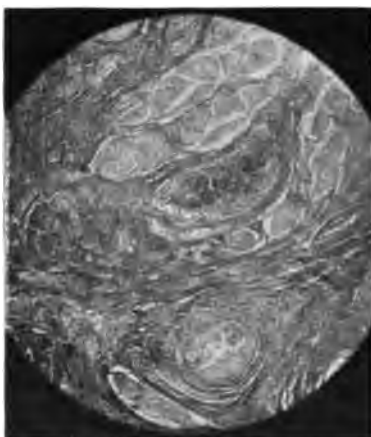


Fig. 2.—Case IV. Tuberculosis of the tongue: multiple tubercles forming a single nodule. Section stained with Weigert-Van Gieson stain. *Photomicrograph* (90 diam.): showing a typical tubercle and a nodule, containing lymphoid cells only, side by side; the lymphoid cells may also be seen invading the connective tissue between the muscle-bundles.



Fig. 3.—Case V. Tuberculosis of the tongue: ulcerating stage. Section stained with Weigert-Van Gieson stain. *Photomicrograph* (100 diam.): showing the margin of the ulcer and containing small-cell infiltration and typical nodular lesions.

itself assumed the form of a “closed” (circumscribed) nodule, in which no changes occurred during a period of ten years.

Case	DATE OF ADMISSION	OFFICE NO.	SEX	AGE	FAMILY HIS- TORY OF TU- BERCU- LOSIS	ACCOMPANYING TUBERCULOUS LESIONS	TRAUMA	CHARACTER OF LESIONS	NUM- BER OF LESIONS*	TIME OF APPEAR- ANCE BEFORE OPERATION	LOCALIZA- TION	GLANDU- LAR IN- VOLVE- MENT (CER- VICAL)	TREATMENT
1	September 28, 1904	939	M.	40	—	..	Smoker (pipe)	Ulcer 8 x 6 x 4 mm.	1	Three months as deep-seated nodule	Left edge 2 cm. from point	+ Bilat- eral	Excision Novem- ber 4, 1904
2	January 22, 1906	1155	F.	30	—	Bronchopulmo- nary tuber- culosis	..	Ulcer 12 x 8 x 6 mm.	1	Three months as deep-seated nodule	Right edge 1 cm. from apex	+ Bilat- eral	Microscopic ex- amination for diagnosis. Cau- tery. January 23, 1906
3	August 6, 1907	A558	M.	46	*	Pulmonary tuberculosis	..	Ulcer 15 x 10 x 5 mm.	1	Two months as superficial nodule	Right edge 2 cm. from apex	+ Bilat- eral	Microscopic ex- amination for diagnosis. Cau- tery. Septem- ber 25, 1907
4	January 28, 1909	A19,632	F.	46	—	Nodule under mucosa	1	Ten years as nodule	Entire right half 2 cm. from point	..	Excision. Janu- ary 29, 1909
5	February 2, 1915	123,733	M.	24	*	Pulmonary tuberculosis	Smoker (pipe)	Ulcer 12 x 6 x 5 mm.	1	Ten months as deep-seated nodule	Right edge 3 cm. from apex	+ Right side	Microscopic ex- amination for diagnosis. Cau- tery. February 2, 1915

In the other cases (I, II, III, V), however, all of which had a personal as well as a family history of tuberculosis, the tuberculous lesion in the tongue very soon (three or four months) reached the ulcerating stage.

It is, therefore, safe to assume that the individual reaction of the body plays a far greater part in defining the histologic picture of tuberculous lesions than the tissue in which the lesion is found.



Fig. 4.—Case V. Stained with Unna-Pappenheim stain. *Photomicrograph* (220 diam.): showing the invasion of the papillary tunica propria by small-cell infiltration and giant-cells.

In the four cases of “open,” ulcerating tuberculosis of the tongue the regional lymph-glands were found to be involved. In Case IV, in which the intralingual granuloma remained intact, no such involvement was found.

Clinical diagnosis was easy in Cases II, III, and V, in which bronchopulmonary lesions were present together with the ulcer of

the tongue; a tuberculous lesion was suspected in Cases I and II. No definite diagnosis could be made (clinically) of Case IV, as no evidence of tuberculosis in other organs could be obtained.

In every case, however, a histologic diagnosis could be made during operation by means of frozen sections, and the histologic findings decided the course to be taken so far as operative and therapeutic treatment were concerned (Figs. 1, 2, 3, 4, and 5).

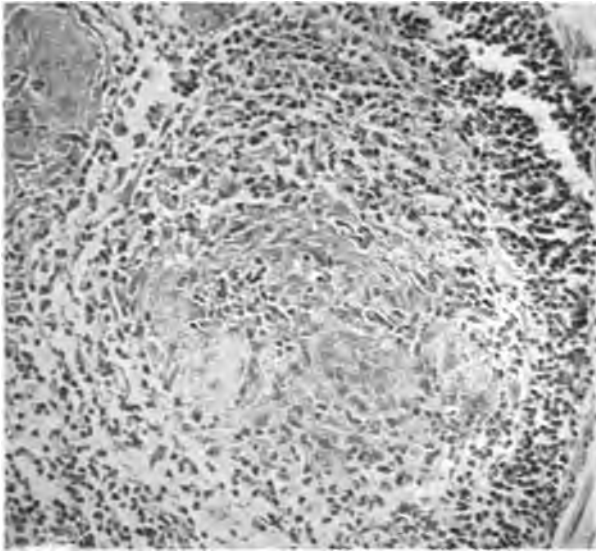


Fig. 5.—Case IV. Histogenesis of the giant-cells. Section stained with Weigert-van Gieson stain. Photomicrograph ($\times 20$ diam.): showing various stages in the formation of giant-cells by the fusion of epithelioid cells, in a large typical tubercle.

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INFECTIONS OF THE MOUTH *

GORDON B. NEW

The most important foci of infection of the body are found in the mouth and upper respiratory tract, including the nose, sinuses, pharynx, trachea, tonsils, gum-margins, tooth-sockets, and jaws. Only infections of the mouth will be discussed in this paper. These may be divided into four groups: (1) Alveolar abscesses; (2) infections about unerupted teeth; (3) infections about ill-fitting crowns, bridges, and fillings; and (4) pyorrhea.

Alveolar Abscesses.—Alveolar abscesses are important foci because of the fact that only a small percentage cause local symptoms, and usually the patients are quite unaware of their existence. Roentgen photographs are essential in locating them; in fact, are the only sure method of determining their presence. These abscesses may be the so-called blind abscesses, or they may be draining through the alveolus. As to their etiology: the infection may occur from the root-canal of a tooth, or it may be hematogenous in origin. Ulrich recently examined, by means of the roentgen ray, a series of jaws of ward-patients, and found that 80 per cent of the dead teeth were abscessed. This was followed by the examination of a similar series of private patients, and an equally high percentage of abscessed teeth were observed, therefore excluding poor dentistry in the ward-patients as the cause of the abscesses. He cultured 159 abscessed teeth, finding streptococci in 150, and believed this an indication that a high percentage of the abscesses were hematogenous in origin, as it would have been impossible for the dentist to infect so many patients with streptococci. Observa-

* Read before the Central State Orthopedic Society, October 13, 1915. Reprinted from the *Journal-Lancet*, 1916, xxxvi, 107-10.

tions in our clinic do not show so high a percentage of alveolar abscesses in the roentgen examination of dead teeth. Many patients are observed, however, in whom the abscesses are about half way up on the root, and with no apparent connection with the apex of the tooth or the gingival margin; and also patients in whom every tooth on one side of the jaw shows abscesses about equal in size. This type seems to be hematogenous in origin. Alveolar abscesses have not as yet been made experimentally in animals by means of streptococci; but the evidence at hand would seem to prove that a large number of these abscesses are due to infection through the blood.

Infection About Erupting Teeth.—Infection about erupting teeth, especially the lower third molars, is a common source of general infection. About one and one-half years ago I had an acute arthritis of the wrist, shoulders, knees, and ankles ten days after a severe infection around an erupting wisdom tooth. The gum-tissue overlapping these partially erupted teeth forms a deep pocket which harbors infection. The irritation of this mucous membrane by mastication frequently causes traumatism; and exacerbations of acute infection are common. The unerupted cuspid tooth is probably the next most likely to give trouble.

Infections About Ill-fitting Crowns, Bridges, and Fillings.—This type of infection is due to the poor dentistry which has been done throughout the country and which has brought very severe criticism on the dental profession as a whole. The crevices formed by these ill-fitting crowns and poorly made fillings irritate the gingival margins, and pockets are formed in which food lodges, and frequently pyorrhea develops from irritation of the gum-margins. All these conditions tend to make a filthy mouth and good media for the development of all kinds of organisms.

Pyorrhea.—The study of this condition has recently been stimulated by articles of Bass and Johns and Barrett and Smith, Bass and Johns holding that the *Amœba buccalis* is the cause of pyorrhea, and that the use of emetin will rid the mouth of the ameba and ultimately cure the condition. The subject has been taken up by many pathologists and dentists throughout the country, but

recent reports are not so convincing as those made by the original investigators.

Sanford and I have studied 327 cases of pyorrhea. These were classified into five groups: pyorrhea 0, 1, 2, 3, 4, depending on the amount of infection in the mouth, and not on the amount of infection about any one tooth or group of teeth. Pyorrhea 0 indicates that the mouth is free from gingival irritation of ill-fitting crowns or fillings. Pyorrhea 1 indicates an early pyorrhea, possibly of the lower incisor teeth. Pyorrhea 2 and 3 are graded in their relative positions; and 4 indicates a very extensive pyorrhea. Smears from the crevices of the gum were made by me, and examined immediately on a warm stage by Sanford. The work of classifying the cases and examining the smears was done separately, and the statistics were not compared until the series was completed.

TABLE

GRADE OF PYORRHEA	NUMBER OF PATIENTS	ENTAMEBA BUCCALIS	PERCENTAGE
0.....	58	8	14—
1.....	51	22	43+
2.....	89	55	62+
3.....	88	63	71+
4.....	41	33	80+
Total.....	327	181	55

Thirty-three cases of pyorrhea were treated with emetin. The ameba was demonstrated in all cases before instituting treatment. Roentgenograms were made; and all abscessed teeth, and all that were too loose to be helped by treatment, were removed. Emetin was given in from one-third to two-third doses of Lilly's ampules or Lilly's Alcestra tablets two or three times a day. Negative smears for ameba were obtained in all the cases in from four to seven days. But little improvement, if any, was noted in the amount of pus present or the general condition of the mouth. These patients were then sent to a local dentist to have all deposits removed and the teeth thoroughly cleaned; no medicines were used. After this treatment, marked improvement was noted.

The rather unsatisfactory results in this group of cases suggested that we try the use of emetin in a second group of cases. The second group constituted cases of pyorrhea that had been extensively treated by local dentists, and by dentists throughout the state, and still showed a great deal of pyorrhea. We selected twenty patients of this type for treatment, but only eight were willing to receive a thorough course of the emetin a sufficiently long period to make their study of any value. Before treatment they were examined by local dentists, who seemed to think that all the local treatment necessary had been given. The ameba was demonstrated, and the patients received emetin, as in the first group, over a period of from two weeks to a month, with results no more encouraging, although the smears became negative for ameba.

While the results in these small series of cases are not convincing, we do believe that the series of cases in which emetin alone was used after thorough dental treatment, and not associated with dental treatment, gave better proof as to its value than the large series in which emetin and the dental treatment were used at the same time. Many of the patients whom we sent to the dentists for cleaning were completely cured by this treatment alone.

Treatment.—It should be borne in mind that during an acute general infection it is not best to attempt to remove the foci of infection, for frequently the general condition is made worse by such treatment. Also, if several abscessed teeth must be removed, or a mouth containing a great deal of pyorrhea is to be treated, it is better to take care of a few teeth at a time with four or five days to a week between, so that the patient may get several small doses of the toxin or vaccine caused by removing abscessed teeth or by treatment, and not one overwhelming dose at a time. The question comes up whether or not abscessed teeth, considered possibly due to secondary infection, should be removed. Most patients feel that the sacrifice of a few teeth is a small matter compared with the possibility of getting relief from the general infection. It is well, however, to be guarded in the prognosis in removing foci of infection in cases of arthritis. The results of the treat-

ment by removing foci seem to classify the cases of arthritis into two groups: first, acute arthritis, rheumatic fever, and pain in joints and muscles; second, chronic arthritis. In the first group the results of removing foci are markedly beneficial; in the second group the patients receive benefit in only a small percentage of cases. In other words, the early cases of arthritis are benefited, while the later cases usually are not, probably due to the amount of pathologic change present.

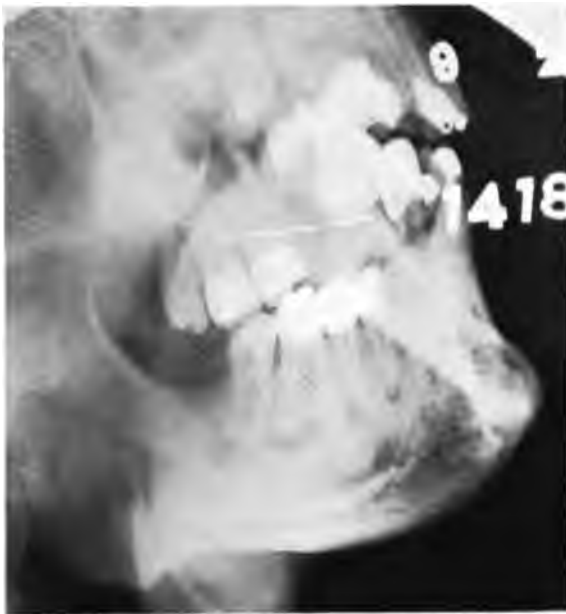


Fig. 6.—Small abscesses around all the lower teeth on one side of the jaw. This type would seem to be hematogenous in origin.

It would seem that in the future the conscientious dentist, knowing the terrible suffering and mortality of the results of the past era in dentistry, would warn patients of the possibility of the presence of dead teeth in the mouth and discuss with them the danger of the use of crowns and bridges. Unless the dentists of today can perfect their technic so as to give all their patients clean

mouths, free from abscesses and gingival irritation, the old-time dentist who extracted teeth and put in plates was really a more

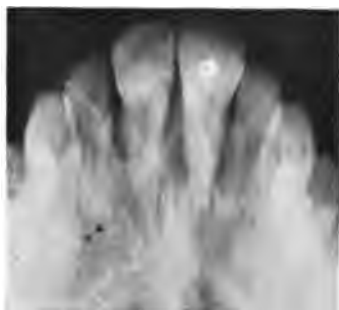


Fig. 7.—Abscess about the central incisor, apparently not connected with apex or gingival margin. The type is possibly hematogenous in origin.



Fig. 8.—Pyorrhea. Large pocket around lateral incisor not demonstrable until roentgenogram was taken.



Fig. 9.—Extensive alveolar abscesses.



Fig. 10.—Multiple alveolar abscesses around incisor teeth.

useful member of the profession, for with his methods the mouth at least was kept free from foci of infection.

The following illustrations show infections in the jaws in cases of arthritis (Figs. 6, 7, 8, 9, and 10).

THE RELATION OF AMEBIASIS TO PYORRHŒA ALVEOLARIS *

ARTHUR H. SANFORD AND GORDON B. NEW

The facts we wish to present are not the result of a study of pyorrhœa alveolaris in its rôle as a source of general infection, but concern the presence of certain protozoan parasites in the mouth and alimentary tract in persons afflicted with this disease.

For the past sixty-five years amebæ have been known to exist in the mouth. Neveu and Lemaire¹ give as the synonyms for *Amœba gingivalis* (Gros, 1849) the terms *Amœba buccalis* (Steinberg, 1862), *Amœba dentalis* (Grassi, 1879), and *Amœba kartulisi* (Doflein, 1901), thus considering that these are all the same organism, and also that they are non-pathogenic. In 1904 Prowazek² described *Entamœba buccalis* and considered it non-pathogenic.

In Braun's³ *Animal Parasites of Man* the subject is treated in practically the same way. As regards the finding of amebæ in the pus of abscesses in the mouth, Braun says: "Doflein conjectures that it was a question of dysenteric amebæ." This statement is interesting and will later be considered in detail.

LeWald's⁴ attention was first called to amebæ in the mouths of Filipinos, and later in this country he found amebæ in the mouths of 71 out of 100 persons on the first examination. He did not make a complete study of their morphology, but considered them identical with *gingivalis* or *buccalis*, and he suggested the name *Amœba oralis hominis*, indicating its constant presence in man.

*Read before the Clinical Congress of Surgeons of North America, Boston, October 25-30, 1915. Reprinted from *Surgery, Gynecology, and Obstetrics*, 1916, xxii, 27-33.

The recent increased interest in the subject has been stimulated by articles by Smith and Barrett⁵ and by Bass and Johns,⁶ independently suggesting that the *Entamoeba buccalis* is the cause of that common disease, pyorrhœa alveolaris. Smith and Barrett found amebæ in all of 46 cases, and found none in seven mouths that were normal. Bass and Johns base their conclusions on the positive findings in more than 300 gross lesions. They state also that there are many other factors to be considered in the etiology of the disease, such as "picking the teeth, cleaning with hard brushes, floss, rubbers, and the effect of hard particles of food between the teeth making pressure on the gums, tartar on the teeth, ill-fitting crowns, etc."

A very complete study of the etiologic factors in the disease has been recently reported by Price.⁷ This work was carried on for the Scientific Foundation and Research Commission of the National Dental Association. The article is exceedingly fair, and weighs all evidence regarding the significance of amebæ in the mouth. He suggests that judgment be withheld until further researches shall have established sufficient data. We quote him as follows:

"The successful production of the lesions of pyorrhœa alveolaris by inoculation with entameba according to Koch's laws . . .

"Or, the successful production of the lesions by inoculation with some other organism or organisms, or by some other means . . .

"Or, the demonstration that the entamebæ of the mouth are non-pathogenic and are incidental or helpful inhabitants of the oral cavity as scavengers; not only harmless of themselves, but not producing either toxins or harmful enzymes . . .

"The establishment of the rôle of emetin including a close differentiation between its amebicidal and its bactericidal actions . . .

"The establishment of the precise local tissue changes involved in the development of the lesion of pyorrhœa alveolaris and of the successive processes constituting its repair. . .

"The establishment of the rôle of pyorrhœa alveolaris pockets as culturing places for pathogenic microorganisms, as those of the streptococcus-pneumococcus group, which from this lesion as a primary focus affect other organs and tissues of the body, and the establishment of the symbiotic effects of the organisms on each other.

"Granting that *Entameba* is the causative factor of pyorrhœa alveolaris and that emetin hydrochlorid is a specific for it, why has no pyorrhœa pocket, of the many cases treated by the authors, been more greatly modified in the way of repair than the more or less marked improvement of the following factors: the quantity of pus flowing; the relative quantity of microörganism growing in the pockets and the general tonicity of the surrounding connective tissues, with practically no considerable change within several months of the bone lesion itself surrounding the tooth?"

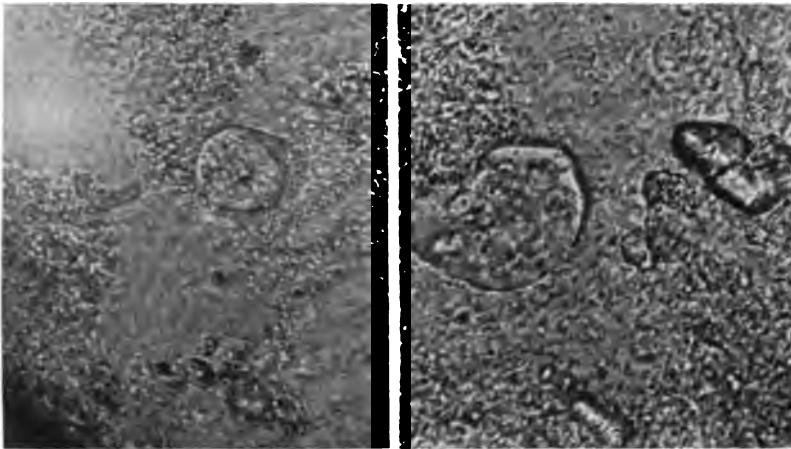


Fig. 11a.—*Entameba histolytica*, warm stage observation.

Fig. 11b.—*Entameba histolytica*, warm stage observation.

For several years at the Mayo Clinic we have been interested in finding amebæ in mouths that showed disease. This work was not carried out systematically and was done purely incidentally in making stool examinations for intestinal parasites. Since January, 1915, however, the work has been conducted in a manner to make statistical study possible. One of us examined the mouths of patients coming for throat examination, and 106 of these were selected for study. Pus about the teeth was drawn into a pipet, a cover-slip preparation made on a slide, and sent to the laboratory for examination. A search for the parasites was made on a warm stage, using a 4 mm. objective. Owing to the fact that there is

usually so much pus, there is very little contrast in the field, and it is more difficult to find them than is the case with amebæ in the stools. However, three or four minutes' search usually results in finding actively motile organisms, with a very clear ectoplasm, and often with several red blood-cells ingested. Their size and morphology are very similar to *Entamoeba histolytica*, found in stools of patients with amebic dysentery. Besides the patients sent primarily to New for examination, a few of those who were having stool examinations were sent to him each morning for mouth



Fig. 12a.—*Entamoeba buccalis*, warm stage observation.



Fig. 12b.—*Entamoeba buccalis*, warm stage observation.

examination. There were in all 221 of these patients, making a total of 327 in the series studied.

The cases have been classified into five groups: Pyorrhea 0, 1, 2, 3, 4, denoting the degree of infection in the mouth that could be demonstrated by an ocular examination and by pressing on the gums to force out the pus. The pyorrhœa 0 group included those in which no sign of pyorrhea could be seen and no pus could be pressed from the margin of the gums. None of these cases showed any gingival irritation from poorly fitting crowns or fillings. Groups 1 to 4 were graded according to the gross amount of infection in the mouth and not on the degree of pyorrhea about one

tooth or group of teeth. Group 1 indicates an early pyorrhea involving possibly the lower central incisor or the molar teeth, while Group 4 includes cases with a very extensive pyorrhea. Groups 2 and 3 were graded in their relative position in the classification, indicating the degree of infection in the mouth. The classification of the patients and the search for the parasites were entirely independent procedures on the part of the two observers, and the results compared only at the time of preparing this report.

Of the total 327 cases, 181 (55 per cent.) showed amebæ in the mouth, all classified as *Entamoeba buccalis* (Prowazek). Of the cases in Group 0 (no pyorrhea), numbering 58, there were 8 (14 per cent.) with parasites (Table I). Amebæ were reported in 43+ per cent. of Group 1 (slight pyorrhea); in 62 per cent. of

TABLE I

GRADE OF PYORRHOEA	TOTAL NUMBER OF PATIENTS	NUMBER WITH ENT-AMOEBA BUCCALIS	PERCENTAGE
0.....	58	8	14—
1.....	51	22	43+
2.....	89	55	62+
3.....	88	63	71+
4.....	41	33	80+
Total.....	327	181	55+

Group 2 (moderate pyorrhea); in 71+ per cent. of Group 3 (advanced pyorrhea); and 80+ per cent. of Group 4 (severe pyorrhea). The relative increase in percentage as the severity of the gross appearance of infection increased is most striking. The significance of this can be interpreted in various ways. By some it may be taken as a direct indication of the specific etiologic rôle of *Entamoeba buccalis* in pyorrhœa alveolaris. We must not overlook, however, the 14 per cent. positive findings in the group with mouths apparently free from infection. Another interpretation of the facts is that there was an increase in percentage of cases directly proportional to the degree of pathologic change in the mouth most suitable for their existence.

Many observers have noted the similarity between *Entamoeba buccalis* and *Entamoeba histolytica*. Smith and Barrett⁴ state: "From a purely morphologic standpoint we are unable to differentiate the organism which we believe to represent the vast majority of oral entamebæ and to occur in an extremely large number of persons not merely in the tropics, but throughout the world, from *Entamoeba histolytica* Schaudinn. We are unwilling to make any assertion which involves biologic identity in full,

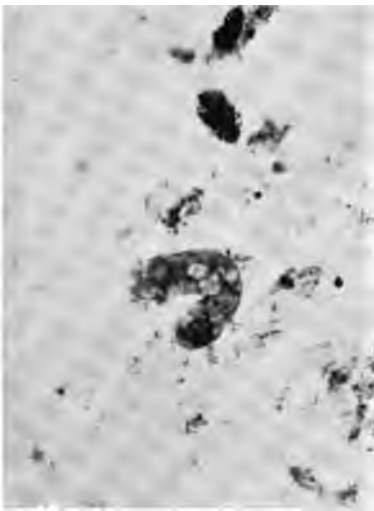


Fig. 13a.—*Entamoeba histolytica*, stained with iron-hematoxylin.

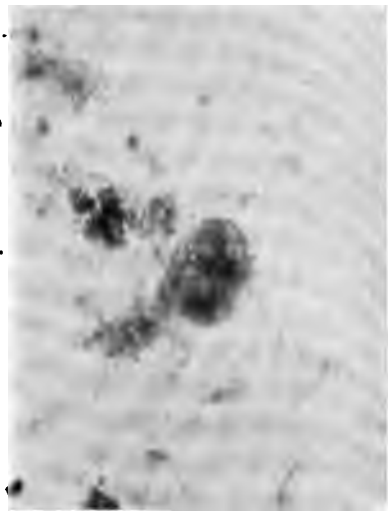


Fig. 13b.—*Entamoeba histolytica*, stained with iron-hematoxylin.

merely asserting that the morphologic similarity is so close that we feel unable to make a distinction from microscopic observation alone. . . . Even if this suggestion be refused, the writers feel that there is need of a more easily demonstrable differentiation, and believe that more than merely morphologic studies are requisite to prove dual specificity."

If these organisms are identical, a large percentage of patients with amebæ in the mouth should show amebæ in the stools, especially if they have chronic diarrhea. It was with the idea of

shedding some light on the relationship between the two types of amebæ that patients with chronic diarrhea, and whose stools were examined first for amebæ, also were examined second for pyorrhea, and third for the *Entamoeba buccalis*. The results are given in Table II.*

TABLE II

		PERCENTAGE	
Total number of cases.....	327		
Total number <i>Entamoeba buccalis</i>		181	55
<i>Entamoeba histolytica</i>	73		
<i>Entamoeba buccalis</i>		31	42+
Other cases.....	254		
<i>Entamoeba buccalis</i>		150	59+
<i>Entamoeba buccalis</i> (patients sent for stool examinations).....	103		
<i>Entamoeba histolytica</i>		31	31

It will be seen from the above table that there were 73 patients with amebæ in the stools, and 254 in which none were found. One hundred six of the 254 were non-diarrheic patients. These had no stool-examinations, as there were no symptoms that made such an examination necessary. Of the 73 patients (stools containing amebæ), 31 (42 per cent.) had *Entamoeba buccalis*, while of the 254 patients (no amebæ were found in the stools), 150 (59 per cent.) were infected with these parasites in the mouth. In other words, there is a smaller percentage of patients with amebæ in their stools that have *Entamoeba buccalis* in their mouths than in the ordinary run of cases.

Still another consideration of this group of cases brings out the fact that of the 221 diarrheic patients sent for mouth examination, 103 had *Entamoeba buccalis* in their mouths, while only 31 (31 per cent.) of these (all patients with symptoms sufficient to warrant a search for intestinal parasites) had *Entamoeba histolytica*. These 221 patients were classified according to the condition of the mouth, as follows: 42 patients with no pyorrhea,

* The universality of amebic dysentery is established. A report on the geographic distribution of amebiasis is in process of preparation.

and 4 of this number with *Entamoeba buccalis* in their mouths; 40 with Grade 1 pyorrhea, 14 with *Entamoeba buccalis*; 59 with Grade 2 pyorrhea, 29 of whom had *Entamoeba buccalis*; 57 with Grade 3 pyorrhea, 38 with *Entamoeba buccalis*; and 23 of the most severe type, or Grade 4, of which number 18 had *Entamoeba buccalis* in their mouths. As mentioned before, of the total number having amebæ in their mouths, only 31 per cent. had amebæ in their stools.

Because of its amebicidal properties, ipecac or its alkaloids has been suggested as a suitable drug for the treatment of pyorrhœa



Fig. 14a.—*Entamoeba buccalis* stained with iron-hematoxylin.



Fig. 14b.—*Entamoeba buccalis* stained with iron-hematoxylin.

alveolaris. In fact, so wide-spread has become its use, that it is now spoken of even by the laity as "the cure for pyorrhea" and its use demanded. Our experience with the drug is limited, but enlightening:

In our first series, 33 patients of varying degree of pyorrhea were treated with emetin. In all where indicated roentgenographs were taken, and teeth showing apical abscesses or teeth about which the disease seemed too far advanced to save were removed before treatment was commenced.

The *Entamoeba buccalis* was demonstrated before treatment was instituted. Emetin was administered either hypodermically,

in $\frac{1}{3}$ to $\frac{2}{3}$ grain doses of Lilly's ampules, or Alcresta tablets (Lilly), two or three times daily. In every instance the smears failed to show the presence of the entameba within four to seven days. On the other hand, we did not observe the marked improvement locally that has been reported from many sources. Some of the patients felt much better generally, but we question if the therapeutic action of emetin does not owe its value to some general effect which has not as yet been demonstrated experimentally by the pharmacologist or recognized by the clinician.

The patients were then sent to have thorough dental surgical treatment without further medical treatment, and after this an improvement was noticed.

Very frequently when no amebæ were found after dental treatment, by waiting four or five days the parasites could again be demonstrated. These would disappear after a few days of treatment, but only temporarily.

The rather unsatisfactory results of this method of treatment suggested that we try the emetin on a group of patients that already had had repeated and thorough dental treatment by competent dentists both locally and throughout the State. Twenty of these patients were examined by local dentists and thought suitable to test the value of emetin, since frequent and thorough instrumentation had failed to cure their pyorrhea. However, only eight of these could be induced to carry out the prescribed course of treatment. *Entamoeba buccalis* was demonstrated in all of them. They were given thorough emetin treatment and the condition of their mouths did not improve. One patient, still under observation, has had 26 injections of $\frac{2}{3}$ grain doses of emetin in addition to thorough dental attention, and there is no improvement. If emetin is the cure for pyorrhea, we believe the specific action should be seen in this manner of treatment.

Though there may seem to be some evidence to the effect that the *Entamoeba buccalis* is a factor in Riggs' disease, yet we feel that Koch's postulates are the ultimate standard by which the specific cause of any infectious disease must be judged. We are thwarted at the outset by the fact that up to the present time para-

sitic amebæ have never been cultivated. However, we thought that it might be possible to find lower animals susceptible to infection with *Entamoeba buccalis* and we carefully examined for parasites the mouths of 18 dogs. Bodonides, flagellate protozoa, were found in three, but in not a single instance were there amebæ. Many of these were old dogs with discolored teeth. Two of this group of animals were selected, and at the juncture of the gingival margin of a molar tooth pus was injected from pyorrhea cases containing amebæ. One dog was inoculated with material from three different mouths, and the other from two patients. After several weeks of observation neither animal showed any signs of pyorrhea, nor could amebæ be found.

Recently we have taken five old dogs and made similar preliminary examinations for protozoa in the mouth, all of which were negative. With a periosteal elevator, pockets were then made about the lower molar teeth, producing considerable trauma. A few days later pyorrhea pus-containing amebæ were placed in these pockets. These animals have also remained negative.

There are many technical difficulties to be considered in any attempt to produce the disease artificially. Dogs are animals with unusually clean mouths and may well be highly resistant to infection. We have also examined the mouths of two rhesus monkeys and found that their mouths are free from pyorrhea and amebæ. Pockets were made around the molar teeth, and pus from several sources containing amebæ was injected. The result in this experiment was also negative.

We recognize the very just criticism that we have in no way disproved the possibility of *Entamoeba buccalis* as the cause of pyorrhœa alveolaris. We do hold, however, that the burden of proof still lies with those who claim the pathogenicity of this organism, and that there should be further attempts to produce the disease experimentally.

Sellards and Baetjer⁴ have reported interesting results in the production of amebic dysentery in cats by performing laparotomies and injecting ameba-containing material directly into the cecum. Following their technic, with the coöperation of Mann, we have

injected five kittens with *Entamoeba buccalis*. These animals have all remained healthy, at no time showing any signs of diarrhea, while two control kittens injected with *Entamoeba histolytica* developed typical amebic dysentery with demonstrable organisms. Guinea-pigs are highly susceptible to amebic infections, but four of these animals injected with *Entamoeba buccalis* showed no signs of dysentery. One died of peritonitis forty-eight hours after operation, but the other three are alive and normal.

At one time during our study of these cases we were very hopeful that the cause of pyorrhœa alveolaris had been found and the cure established. At present, our opinion, based on statistical and experimental study, may be expressed in the following conclusions:

1. *Entamoeba buccalis* is found in at least 14 per cent. of mouths free from gingival irritation, and in relatively increasing numbers in accordance with the degree of pyorrhea as we have classified them.

2. Clinically there is no parallelism between the presence of *Entamoeba buccalis*, the parasite ameba of the mouth, and *Entamoeba histolytica*, the cause of amebic dysentery.

3. We believe that before the alkaloids of ipecac can be accepted as the cure of pyorrhœa alveolaris it must be established that they actually destroy the amebæ in the mouth, thus removing the cause of the disease.

4. Our experiments, few as they are in number, with Sellard and Baetjer's technic of intracecal injection, convince us that *Entamoeba buccalis* and *Entamoeba histolytica* are not the same organism. We also hold that before *Entamoeba buccalis* is called the cause of pyorrhœa alveolaris its pathogenicity must be demonstrated by animal experimentation.

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BILATERAL PAROTID TUMORS

GORDON B. NEW

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Bilateral parotid tumor is a general term applied to bilateral enlargement in the parotid region. It may be true salivary gland tumor or regional lymphoma, due to various causes. Unilateral parotid tumor is not an uncommon condition, and is most frequently seen as mixed tumor of the parotid, tuberculous glands in this region, parotid cyst, or as an infection of the parotid. Bilateral parotid tumor, however, is a more unusual condition. The following is a report of classified cases which have come under my personal observation:

1. Recurrent bilateral parotid tumors.
2. Syphilitic bilateral parotid tumors.
3. Tuberculous bilateral parotid tumors.
4. Bilateral parotid tumors associated with leukemia.
5. Mikulicz's disease.
6. Bilateral parotid tumors due probably to a local infection.

Recurrent Bilateral Parotid Tumors.—CASE 101,152.—A. C. P., woman, aged forty-seven, married. Examination February 24, 1914. Family history negative. She has three children: has had no miscarriages. Thirty years ago she had walking typhoid. A swelling in front of each ear was first noticed three and one-half years prior to examination, coming on about three weeks after the birth of a child. Both sides swelled up in a day, and she could not open her mouth. The swelling remained for two days and then subsided. During the next year these swellings, up to the size of a small orange, appeared coincident with a cold, and in a few days disappeared entirely. During the past year the swelling appeared in about the same manner and size, except that during the intervals a small tumor remained. When the patient comes in

contact with a cold wind, the swelling recurs, but recedes in an hour or so. The condition is also brought on by eating sour foods. The mouth is generally dry; the other salivary glands are never enlarged. The patient is a healthy looking woman, weighing 107 pounds. Blood-pressure, 125 and 80; pulse, 72; temperature, normal. In front of both ears were soft, elastic, freely movable, symmetric tumors, about the size of half a lemon, not inflammatory, not tender. The other salivary glands and lacrimals not enlarged. Examination of the nose, throat, and mouth revealed nothing of note. Both Stenson's ducts were open and secreting normal-looking saliva. No enlargements were palpable in the ducts. Wassermann negative. Red blood-cells, 4,380,000; white,



Fig. 15.—Recurrent bilateral parotid tumors.

4100. Small lymphocytes, 43.2 per cent.; large lymphocytes, 12.7 per cent. Polymorphonuclears, 44; eosinophils, 7; basophils, 3. The condition is probably due to a narrowing of the duct so slight that, under ordinary conditions, the saliva passes quite readily. The extra amount of saliva secreted under stimulation of the cold air or sour food is dammed back, causing enlargement of the glands. Early in the history of this case a catarrhal condition of the duct during a cold caused the obstruction of the saliva and thus the parotid enlargements (Fig. 15).

Friedberg¹ reports a case of recurrent swelling of the parotid due to the taking of acid foods. The swellings were not painful,

but the tumors persisted between the attacks. The condition was of fifteen years' duration, and the discharge from the ducts was normal. Friedberg believes that in his case the condition was due to spasmodic closure of the duct brought on by a stimulation of certain foods. In 1896 Johnson² reported five cases of swelling of the parotid coming on during a meal. He demonstrated obstruction of Stenson's duct causing retention of the saliva. Hewlett³ reports a case of bilateral intermittent swelling of the parotids of nine months' duration due to infection of Stenson's duct. A mucopurulent discharge could be obtained from the mouths of the ducts. In these cases the condition cleared up by the use of argyrol in the ducts and frequent massage of the glands. The question of a stone in the duct or thick mucus obstruction must be thought of in this type of case.

Syphilitic Bilateral Parotid Tumors.—(CASE A92,601.—D. McK., woman, aged forty-three, married. Examination September 25, 1913. Family history negative. She had two healthy children, eighteen and twelve; one miscarriage nine years ago. No previous illness of note. Denies venereal disease. Six years prior to examination she noticed small tumors in front of both ears starting at the same time. They were soft and freely movable and not painful. The one near the left ear was removed soon after its discovery, at which time it was about the size of a small plum. It recurred in a short time and was again removed one year ago. Following the operation a facial paralysis was noticed. The tumor on the right side was operated on three times, each time with recurrence; the last operation, one year ago, with recurrence six months later. The tumor is now increasing in size. No medical or other treatment has been used. The patient complains of dryness of the mouth, but her general health is good. Examination revealed a tumor of the right parotid region, soft, elastic, and freely movable, 2.5 x 2.5 x 2 inches in size, extending in front, below, and back of her ear. There were scars on both sides of the neck from previous operations. No other salivary glands were enlarged. The mouth and tongue were dry, as was the mucous membrane of the pharynx and larynx. Argyll-Robertson pupil of the right eye; in the left the reflexes were normal; muscles were normal. There was partial facial paralysis of the left side; knee-jerks not

brisk, but present; no general signs of tabes. Wassermann positive. The patient was given three doses of salvarsan. In a month the tumors were markedly reduced in size, and within six weeks were scarcely noticeable. There was much general improvement. This is apparently a case of definite regional lymphoma of syphilitic origin.

Claus⁴ says that luetic enlargement in the parotid region is a rare condition, but of all the salivary glands, the parotid is the most frequently enlarged. This usually occurs in the second stage of lues. Letulle and Vuillet⁵ state that syphilis in the parotid region is a very rare condition. They report one case of a man, aged forty-nine, who had had a unilateral parotid tumor on the right side for two years. The left parotid was quite normal, and no other glands were enlarged. Secretion from the glands was normal. The general examination was negative; Wassermann test strongly positive; total inhibition. A specimen was excised for diagnosis and the ulcer resulting did not heal. By the use of biniodid of mercury injections and salvarsan the tumor cleared up entirely. Simard⁶ reports a case of unilateral syphilitic parotid tumor in a man, aged seventy-four, who had had a chancre at the age of forty. Four weeks later he developed a smooth parotid tumor the size of a hen's egg. No other glands were affected; there was no affection of the mouth or nose. Specific treatment was instituted, and in eight days improvement was noticed; in fifteen days the tumor had almost entirely disappeared. It would seem from these reports that syphilis of the parotid yields quite readily to antisyphilitic treatment.

Tuberculous Bilateral Parotid Tumors.—CASE 94,994.—A. McB., man, aged eighteen, single. Examination November 5, 1913. Previous history not important. No history of tobacco or alcohol. Chief complaint, swelling of both sides of face in front of the ears. Seven weeks previous to examination a swelling started on the right side of the face in front of the ear. Two days later a swelling started on the left side. These swellings were never sore nor painful. There was no enlargement of the submaxillary, sublingual, nor lacrimal glands. For past five years

he has noticed that his eyes were red and inflamed at times. There had been some nasal obstruction for the last year. He had an operation three weeks before coming for examination. A specimen was removed from the right parotid region, and a diagnosis made of von Mikulicz's disease. For the past five weeks tuberculin, but no specific treatment, has been used. General health good. The patient is fairly well nourished, 5 feet 6 inches in height; weighs 150 pounds; no loss. There are hard nodular tumors in both parotid regions, extending in front of the ears and into the mastoid region; freely movable, not tender, and regular in outline. Scattered hard glands the size of beans and peas were found in the left supraclavicular region, and two small glands in the right groin. There was a scar over the right parotid region from the operation for removal of the specimen. Slight fibrous thickening was found in the roentgenograms of the chest. Hemoglobin, 89 per cent.; red blood-cells, 4,800,000; white blood-cells, 3800. Examination of the eyes showed a low-grade iritis, probably tuberculous. The septum was deflected; there were rhinitis and pharyngitis; the tonsils were of medium size. There were no signs of chronic infection; Wassermann negative. Potassium iodid was given internally to 60 drops, and mercury ointment was rubbed into the skin over the glands daily. For the iritis atropin was put in the eyes. After two weeks of this treatment the glands began to soften and showed signs of disappearing. On December 17, 1913, the left tumor had almost disappeared, and the one on the right was just palpable. Second Wassermann negative. The pupils were easily dilated with atropin, but the ciliary injection remained. On December 18, 1913, a definite tuberculous kerato-iritis developed in the right eye.

Because of the character of the glands and the definite tuberculous condition of the eyes it seems probable that this case should be classified as regional lymphoma of tuberculous origin.

Homuth⁷ reported one case and reviewed the literature on the subject (about 21 cases). He states that tuberculosis of the parotid rarely occurs, and that differentiation must be made from chronic inflammatory tumors, malignant tumors, gumma, and mucous cyst of the parotid, and that the prognosis is favorable except in cases of general tuberculosis. He states further that the condition may be bilateral. This report refers to tuberculosis of the substance of the salivary gland. Cole⁸ reports a case of bi-

lateral soft swelling in the parotid region in a man, aged thirty-four, with positive luetic history, in whom tuberculous glands had been removed from the neck. A complete diagnosis had not been made at the time the case was reported.

Bilateral Parotid Tumors Associated with Lymphatic Leukemia.—CASE 123,094.—C. B., woman, aged fifty-five, married. Examination January 22, 1915. This woman came to our clinic for bilateral swellings in front and about the ears which started two years before, following bronchitis. The swellings had enlarged to the present size in one month, but had not changed since. The enlargements had never been tender nor painful. No sore throat nor nasal trouble. The patient's general health is good; she came for treatment for the cosmetic effect. Two and one-half years prior to examination she noticed a swelling of the left leg and foot which lasted about three weeks, and was followed by a slight swelling of the right leg which lasted for a short time. A large ulcer formed from scratching, which soon healed. About two years later the ulcer returned and still exists, but seems to be healing. There was an eruption on the knees and thighs several years ago, which she believed to be eczema. The patient looks healthy and weighs 175 pounds. Systolic blood-pressure, 180; diastolic, 100; pulse, 80; temperature, normal. Tumors soft and elastic in front and below both ears. Mouth dry and red, as were the pharynx and tongue. Small ulcers on the front of right leg. Wassermann strongly positive; total inhibition, which still exists. Hemoglobin, 78 per cent.; red blood-cells, 4,600,000; white blood-cells, 171,200; number of cells counted, 300; polynuclear neutrophils, 0.4; small lymphocytes, 87.3; large lymphocytes, 8.3; eosinophiles, 0.3. Roentgenogram negative for the chest, with slight enlargement of the heart to the left. A second examination of the blood on February 13, 1915, showed hemoglobin, 65 per cent.; red blood-cells, 3,890,000; leukocytes, 140,000; number of cells counted, 300; polynuclear neutrophils, 8; small lymphocytes, 89 per cent.; large lymphocytes, 3 per cent.; slight anisocytosis and slight polychromatophilia. There were no enlargements of the salivary or lacrimal glands. This patient was given several injections of salvarsan, but on March 22d, two months after the beginning of the treatment, the tumors had not shown any decrease in size. This is apparently a case of bilateral parotid lymphoma with lymphatic leukemia as the cause (Fig. 16).

Tileston⁹ describes a case of a child, aged two, with lymphatic leukemia and enlargement of the parotid and submaxillary glands. He finds lymphatic leukemia associated with enlargements of this type in the parotid and submaxillary region to be an extremely rare condition. He says that the diagnosis of Mikulicz's disease should not be made in these cases of bilateral symmetric enlarge-



Fig. 16.—Bilateral parotid tumor associated with lymphatic leukemia.

ment of the salivary glands unless pseudoleukemia and leukemia have been excluded.

Mikulicz's Disease. — CASE 112,299. — Man, aged fifty. Examination August 6, 1914. Twenty-nine years previously tumors of the submaxillary region appeared on the right side. They were first noticed from the parotid region, then extended to the mastoid region. Eight years prior to examination the tumors were removed, but during the last two years tumors have been

extending into the submaxillary and submental region on both sides. These tumors had been removed. The man is well nourished, with soft, elastic, freely movable tumors of both parotid regions extending back toward the mastoid and below the jaws to the submaxillary and submental regions. The right side is somewhat larger than the left. The scars of previous operations are present over several areas of the tumors. Wassermann negative. At operation a portion of the left parotid tumor was removed. Pathologic examination showed Mikulicz's disease, a pure lymphoid hyperplasia (Figs. 17, 18, 19).



Fig. 17.—Mikulicz disease.

CASE 90,111.¹⁰—J. A., man, aged forty-seven, married. Examination August 15, 1913. Previous history not important. Uses alcohol and tobacco. Neisserian infection twelve years prior to examination. He complains chiefly of swellings of the face, mouth, and lids. Five years ago swelling appeared under the lower jaw; six months later on the right side; eighteen months ago over the eyes, and six months ago in the axillæ and groins. The swellings have never been red nor painful. His voice for three years has been somewhat husky. For the past two years there

has been slight difficulty in breathing; no dysphagia. The swellings have increased in size slowly and progressively to the present time. He sleeps a great deal, and for the last six months has done no work on account of general weakness. He has some slight dryness of the mouth lately, but no insufficiency of tear production. Normal weight, 205 pounds; present weight, 170 pounds. This loss of weight is said to have occurred during the last year. The lacrimals and accessory lacrimals, sublinguals, and submaxillary and parotid glands are all greatly enlarged, the enlargements being symmetric. The tumors are smoothly rounded, somewhat



Fig. 18.—Mikulicz disease.

elastic, not fluctuating, and not inflammatory. The tonsils are greatly enlarged. On account of the enlargement of the lacrimal and accessory glands the lids show considerable ptosis, and the eyeballs are somewhat pushed forward, though their motion is unimpaired. The groins and axillæ present glandular enlargements the size of small beans. The chest and abdomen are apparently perfectly normal, except for enlargement of the heart. The roentgen ray, however, reveals considerable mediastinal thick-

ening. The ears are much retracted, probably from pressure on the Eustachian tube. The turbinates are considerably engorged; eye-grounds and reflexes normal. Hemoglobin, 69 per cent.; reds, 4,200,000. Number of leukocytes, 8200, of which small lymphocytes, 16.3 per cent.; large lymphocytes, 4 per cent.; polymorphonuclears, 79.3 per cent.; eosinophiles, 0.3 per cent. There is very slight variation in the size of the red cells. Speci-

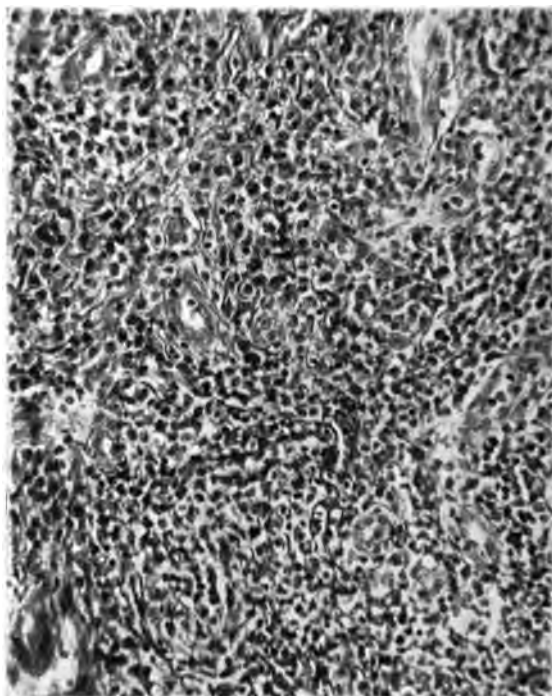


Fig. 19.—Photomicrograph. Mikulicz disease. Parotid salivary gland. Marked lymphoid hyperplasia; only few salivary acini remaining.

mens were taken from the submaxillary region, and the lacrimal glands were entirely removed for diagnostic purposes. Microscopically, the tumor consists almost entirely of lymphoid cells of rather large size. These show a moderate increase of mitotic figures. The tissue does not show any definite arrangement, though here and there are found septa of connective tissue, and in one or two places apparent formation of new connective tissue,

with an occasional fibroblast. No remnants of glandular tissue or ducts are visible in any part of the tumor, although the tumor comprises the whole of what was the gland, being inclosed in the old glandular capsule. No eosinophiles nor chronic inflammatory cells are present. The blood-vessels are fairly numerous and do not show any significant changes. Staining for bacteria gives a negative result.

In reporting this case Fisher¹⁰ thoroughly covered the literature on the subject.



Fig. 20.—Mikulicz disease.

Bilateral Parotid Tumors due to Local Infection.—CASE 94,876.—M., woman, aged fifty-two, married. Examination November 4, 1913. Family history negative. She has six children, youngest twelve and oldest thirty; has had two miscarriages. There were swellings of both sides of the face in front of the ears. Four years prior to examination she first noticed swelling in front of the right ear. There had been a small kernel just below the lobe of the right ear for years. This did not appear to increase in size,

but the tumor in front extended back to it. If the patient had a cold, she noticed a slight increase in the tumors and a full feeling in this region. About six weeks ago she noticed a swelling, movable and soft, in front and below the left ear, about the size of a lima-bean, which rapidly increased in size. The one on the right side increased still more rapidly (one-third). There was no dryness of the mouth, no general complaint. The woman is well

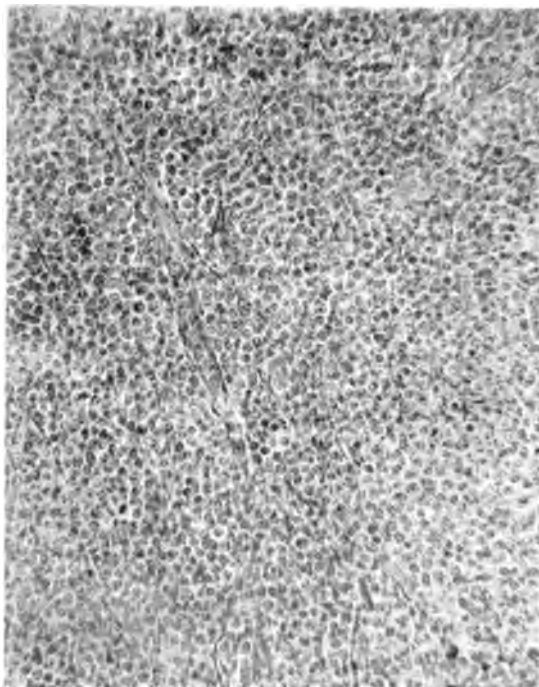


Fig. 21.—Photomicrograph. Mikulicz disease. Parotid salivary gland. Marked lymphoid hyperplasia with complete destruction of salivary parenchyma.

nourished, is 5 feet 4.5 inches tall; usual weight, 117 pounds; present weight, 128.5 pounds. Soft and elastic bilateral tumors in both parotid regions; on the right side, 2.75 x 2.5 x 1.5 inches; on the left side, 2.5 x 1.5 x 1 inch. No other glands palpable; no other salivary glands enlarged. Mouth, nose, throat, eyes, and knee-jerks normal. Wassermann negative. The patient was given potassium iodid and mercury, but without any effect on the

glands. She was examined recently, and it was found that the glands had not changed since the first examination (Fig. 22).

The etiology of this case is questionable, but in all probability the condition is secondary to an infection in the nose or throat. The increase in the size of the tumor is definitely associated with a cold in the head. Cases have been noted of Parinaud's conjunctivitis with bilateral lymphatic enlargement in the parotid region.



Fig. 22.—Bilateral tumors due to local infection.

Diagnosis.—The study of these various types of bilateral enlargements of the parotid region, and especially a consideration of the lymphoma type, is interesting. Poirier, Cuneo, and Delamere¹¹ state that the lymphatic glands in the parotid space are situated either external to the parotid gland, immediately beneath the parotid fascia, or in the actual substance of the gland. Thus the differentiation of lymphatic enlargements in this region from actual gland tumors is sometimes impossible. The parotid group of glands drains the external surface of the ear, external auditory canal, tympanum, skin over temporal and frontal regions, eyelids, and the root of the nose, the mucous membrane of the nose, and

the posterior part of the alveolar process of the upper jaw. From this it would seem that the possibility of any infection in this region draining into the glands must be considered.

Warthin¹² classifies lymphatic enlargements as primary, secondary, or hematogenous. The primary type may be local or generalized, and of this type the malignant lymphoma of Hodgkin's disease is probably the most frequently seen. It would seem that the two cases of Mikulicz's disease and the case associated with lymphatic leukemia should be, according to the evidence at hand as to the etiology of these conditions, in this group. Secondary enlargements are the most common type, as in the infection of a group of glands from some local infected foci within the region tributary to them. In the hematogenous infection of the lymphatics usually several groups of glands are involved, although local glandular enlargements may occur. The case of syphilitic tumors should be classified in this latter group. Whether the tuberculous case would come under this grouping or under the secondary lymphatic group would be a question.

The diagnosis is based on the general examination, the Wassermann test, and the blood count, as well as an examination of the tumor and any local condition in the special organs of the head.

Mikulicz's disease is a bilateral, smooth, symmetric enlargement of the salivary and lacrimal glands in pairs or of all. Microscopic tissue shows a pure lymphoid hyperplasia, although some reports of cases have varied in this picture. It would seem that this term, if the disease is an entity, should be reserved for those cases in which leukemia, syphilis, tuberculosis, and chronic infection of the glands have been excluded as far as it is possible to do so. This is most important, especially when the parotid glands alone are enlarged.

Treatment.—The treatment of these cases necessarily depends on the etiology of the individual case. The recurrent tumor in this series was treated by prophylactic measures, absence of foods that stimulate the secretions, and precautions for protection when going into cold air. Thus treated, any enlargement of the tumors can be prevented. The tumor, under antispecific treatment,

salvarsan, potassium iodid, and mercury, was hardly noticeable in six weeks. With the use of the blue ointment locally the tuberculous patient improved for a time, but a letter from the patient recently stated that the condition had not improved of late, although the same treatment had been continued. The case associated with lymphatic leukemia in connection with a strong positive total inhibition Wassermann was put on the antispecific treatment, but did not improve with two months of treatment. The treatment for Mikulicz's disease is empirical, as at the present time the etiology is not known. Portions of the tumors may be removed for cosmetic effect, although usually the tumor gradually returns to its original size. At the present time radium and the roentgen ray seems to be of the most value.

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STUDIES IN SURGERY OF THE TONSIL

II. Tonsillectomy *

JUSTUS MATTHEWS

Complete removal of the tonsil in its capsule with the least possible danger and discomfort to the patient is the cardinal requirement of any operation on the tonsils. The instruments used in our clinic are a syringe with extension barrel and curved needle, the Robertson knife, Richards forceps, and Tydings snare. The tonsils and the mucous membrane immediately surrounding them are brushed with cocain (10 per cent.), and this is repeated in five minutes. After a like interval a solution of novocain ($\frac{1}{4}$ per cent.) with one minim of adrenalin per dram is injected into the connective tissue about the capsules. When the patient pales from the effect of the adrenalin, the operation is commenced. The tongue is depressed until the edge of the palatoglossus is prominent in the anterior pillar. Immediately behind the pillar appears a triangular depression whose other side is the tonsillar portion of the plica triangularis, and whose base is the root of the tongue. The point of the knife is placed in this depression and swept upward in such a manner as to cut the mucous membrane and enter the deeper tissues between the capsule and the anterior pillar. The incision is continued upward until the superior pole of the tonsil is reached, when the knife is turned slightly and brought down between the capsule and the posterior pillar. While this incision is being made, the tissues are not fixed by the forceps, and, as the knife follows accurately the line of least resistance, there is little or no danger of wounding the muscles surrounding the tonsil.

* Abstract of article read before the American Medical Association, San Francisco, June 23, 1915. Reprinted from Jour. Amer. Med. Assoc., 1916, lxvi, 503-504.

This single incision is usually sufficient to free the superior pole, so that it may be grasped by the forceps and drawn inward and downward. While the capsule is thus put under considerable tension, the fascia and muscle are pushed away from it with the flat surface of the knife. The process is continued until the entire surface of the capsule, including the insertion of the superior constrictor

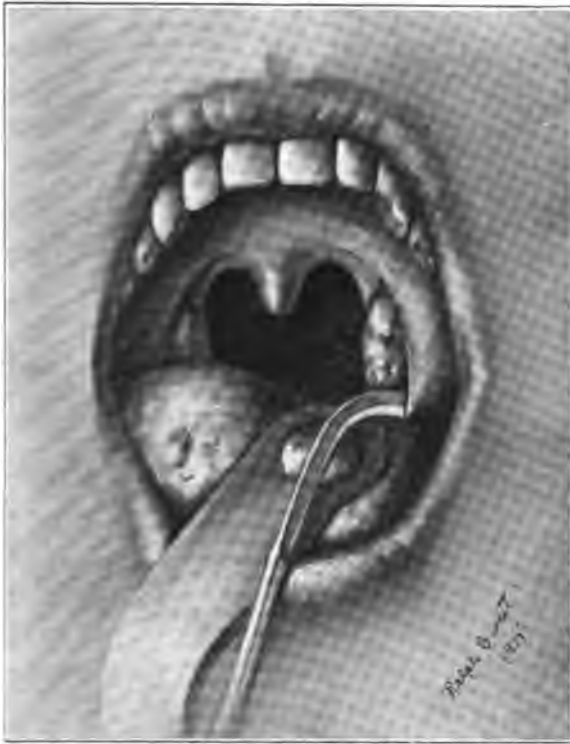


Fig. 23.—Point at which incision is made.

muscle, has been freed, so that the tonsil is attached only at the lower aspect of the inferior pole. Then the snare is passed over the forceps and tonsil in such a manner that the free end of the loop engages the remaining attachment and the lymphoid tissue which appears on the folds of the mucous membrane below it.

The lymphoid tissue should be carefully removed, as it fre-

quently contains crypts which are capable of furnishing the source of local and general infections. This point has been mentioned by Thayer and others, but does not receive the attention it deserves. Within the last year I have seen several patients who suffered from recurring sore throat from this source, and at least three patients



Fig. 24.—Condition of tonsil after incision has been carried up along anterior pillar over upper pole and down along posterior pillar.

in whom symptoms of rheumatoid arthritis persisted after tonsillectomy, but disappeared promptly after the excision of subtonsillar lymphoid follicles containing suppurating crypts.

The blood-vessels entering the tonsil that are necessarily severed by tonsillectomy are much smaller than those in the fascia

in contact with the capsule. The latter are liable to injury by the use of a sharp instrument when separating the tonsil from the peritonsillar tissues, but by the method described the fascia is pushed away with the flat surface of the knife and unnecessary hemorrhage usually avoided (Figs. 23, 24, 25, and 26).



FIG. 25.—Forceps grasping over superior pole and drawing tonsil into pharynx. Knife pushing deeper fascia away from capsule.

During the operation the tonsillar branches of the glosso-pharyngeal nerve are frequently seen as small filaments which emerge from the fascia and enter the capsule at one or more points, while the main branches remain hidden by the superior constrictor

muscle. This is the normal condition, but occasionally other filaments proceeding to the lower pharynx and the larynx of the base of the tongue may be seen. In rare instances the entire terminal portion of the glossopharyngeal nerve pierces the superior con-



Fig. 26.—Snare passed over tonsil and forceps to separate mucous membrane and lymphoid tissues below inferior pole.

strictor muscle at the insertion of the stylopharyngeus, and thence to the base of the tongue lies in direct contact with the capsule of the tonsil. In this situation these nerves are liable to be cut during operations for complete removal of the tonsils, but are not within the field usually exposed by tonsillotomy. Here we find the

explanation of the fact that vocal disability following operations on the tonsils has usually been associated with complete removal of the tonsils with little deformity, while shocking mutilations may be seen with no functional impairment.

I have recently seen a woman, operated on elsewhere one and one-half years ago, who came complaining of discomfort and dryness in one side of the pharynx and difficulty and rapid fatigue in speaking or singing. Several laryngologists had reported the operative results perfect, and as on first observation the tonsillar fossæ were clean, my opinion agreed with theirs. The muscles of the palate, pillars, and tongue were uninjured, and there was a minimum of scarring. On subsequent observation, however, I found on one side the root of the tongue depressed, the muscular action impaired, and the papillæ and mucous membrane noticeably atrophied. As only loss of innervation could cause such changes, and as the symptoms followed were the results of tonsillectomy, there is little doubt that the terminal branches of the ninth nerve were severed. This patient's complaint was typical, and it seems reasonable to assume that others have suffered from the same cause.

One tonsillectomy patient of my own and one who had been operated on elsewhere and came under my observation had clean tonsillar fossæ and no visible cause for pain, but they suffered with severe neuralgia in the nerves at the juncture of the palatoglossus muscle with the tongue. In a large percentage of cases a short section of the terminal portion of the glossopharyngeal nerve is exposed at this point and liable to injury in removing the tonsil. Since no other lesions can explain the severe pain, I have concluded that such an accident is the probable cause, and have recommended, though without opportunity of trying it, injection of alcohol into the trunk of the nerve.

THE BACTERIOLOGY OF ULCER OF THE STOMACH AND DUODENUM IN MAN *

EDWARD C. ROSENOW AND ARTHUR H. SANFORD

It is recognized that hemorrhage of the stomach with or without visible ulceration occurs rather commonly during the late stages of severe streptococcal infections in man and animals. The cause of the gastric lesions in these cases usually is thought to be the profound toxemia, in spite of the fact that many observers have demonstrated the presence of streptococci or diplococci in the lesions in the mucous membrane. The cause of the usual ulcer of the stomach in man, which tends to persist and which occurs commonly in otherwise healthy individuals, the usual symptoms or other evidences of infection being slight or wholly absent, is not clearly established. The presence of pyorrhea, as noted by Bolton¹ and others, of blind abscesses about the roots of teeth, of chronically infected tonsils and sinuses about the head; the occurrence of acute attacks of such infections, especially streptococcal, often a week or ten days previous to acute ulceration and previous to exacerbation of symptoms in chronic ulcer; the aggravation of symptoms in chronic duodenal ulcer during the months when throat and other streptococcal infections are particularly prevalent, as emphasized by Moynihan²; the improvement in symptoms following eradication of foci of infection, as noted especially by Billings³; and the fact that streptococci, when of a certain grade of virulence, quite irrespective of their original source, are prone to localize in the mucous membrane of the stomach and duodenum of animals following intravenous injection, producing ulcers which

* From the Memorial Institute for Infectious Diseases, Chicago, and the Mayo Clinic, Rochester, Minnesota. Reprinted from *Jour. of Infectious Diseases*, 1915, xvii, 219-226.

resemble those in man, as shown by Rosenow⁴—all suggest strongly that a localized streptococcal infection may be an important factor in the original production of the ulceration.

Heretofore, the cultures of ulcers of the stomach have been made chiefly after death and from the floor of the ulcer, and not usually from the emulsified tissues remote from the ulcerated area. The results, as should be expected, have been so unsatisfactory as to lead to a general belief that bacteriologic examination of ulcers as they occur in man cannot be made with any degree of satisfaction. However, a systematic bacteriologic study of the emulsified tissues surrounding the ulceration, removed during life at operation, should yield more trustworthy results.

In this paper we wish to record the results of cultures and of the histologic examination of the tissues in a series of ulcers and lymph-glands draining the ulcers, excised at operation. We wish here to express our appreciation of the opportunity afforded us in the willing coöperation of Dr. W. J. Mayo, Dr. C. H. Mayo, Dr. E. S. Judd, Dr. D. C. Balfour, Dr. A. J. Ochsner, Dr. A. D. Bevan, Dr. L. L. McArthur, and Dr. C. H. McKenna.

TECHNIC

The ulcers and other tissues were excised under strictly aseptic precautions, covered at once with sterile gauze, and cultures made as soon as possible thereafter, usually within one to three hours. After some of the material from the floor of the ulcer, in suitable cases, had been withdrawn into a sterile pipet (for control cultures) and the surface of the ulcer thoroughly washed in running, sterile water, approximately one-half of the ulcer was excised with a small, sterile scalpel, the incisions being made from the normal tissue toward the center of the ulcerated area. The excised part was again washed thoroughly in sterile water or salt solution and the emulsion prepared in the sterile air-chamber directly if the size of the tissue was small, or after the surface had been sterilized with passing through a very hot Bunsen flame or with a searing blade, if the piece of tissue was large enough. Cultures were made in some instances in the same way from the adjacent normal wall and in a number of instances from the indurated area far removed from the ulcerated surface and from the

overlying mucous membrane. The lymph-glands and other tissues were treated in a similar manner.

The emulsions were prepared in dextrose broth or NaCl solution, and the cultures made chiefly in tall columns (9–12 cm.) of dextrose agar and broth, with and without the addition of sterile ascites fluid, and on Loeffler's blood-serum and ascites agar slants, as described by Rosenow.⁵

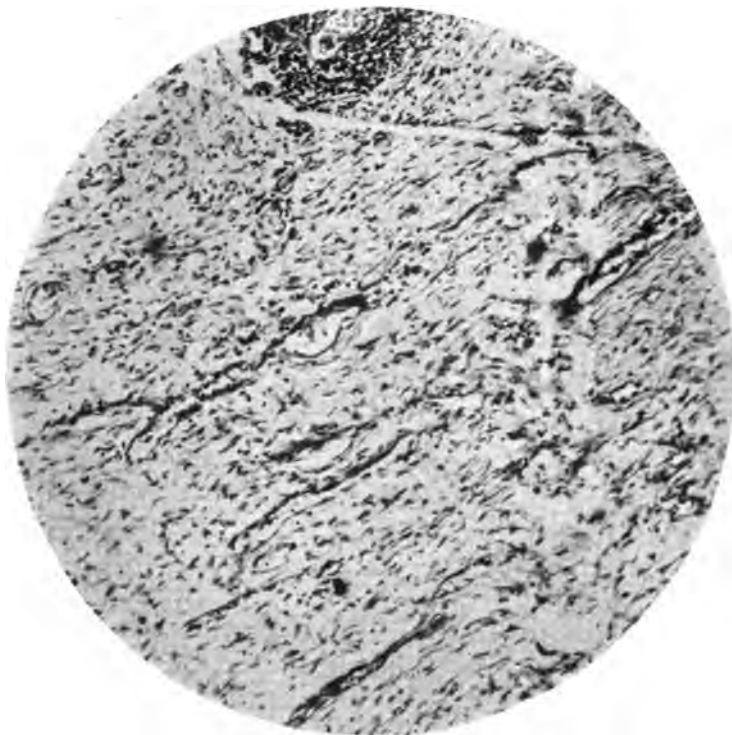


Fig. 27.—Section of chronic, indurated ulcer of the stomach in a man twenty-seven years of age. Note the connective tissue, with little or no cellular infiltration, and the marked round-cell infiltration around blood-vessel ($\times 80$).

The portion of the ulcer saved for microscopic study was fixed in alcohol or 10 per cent. formalin, embedded in paraffin, stained with hematoxylin and eosin, and for bacteria by the Gram-Weigert method. In this method complete decolorization was not practised, because it was found that streptococci present were very easily decolorized; hence decolorization was carried to a pale blue only.

Cultures have been made from ulcers or regional lymph-glands or from both in 32 cases. In 15 the ulcer was situated in the pyloric end of the stomach, in 5 at the lesser curvature, in 3 in the fundus, and in 12 in the duodenum. In 3 cases there were ulcer of both the stomach and the duodenum. Chronic appendicitis was associated with ulcer in 7 of the cases, cholecystitis in 5, and pancreatitis in 3. Appendicitis, ulcer, and cholecystitis coexisted in 2 cases; ulcer, cholecystitis, and pancreatitis in 1 case. The age of the patients ranged from twenty to seventy-two years. The



Fig. 28.—Diplococci in peritoneal coat of ulcer of the duodenum (see Case 112 in Table 1).

duration of the symptoms of ulcer at the time of operation ranged from six months to twenty-three years.

Cultures were made from the wall of ulcers in 24 cases. In these, streptococci were isolated in varying numbers (1:5000 colonies) in pure culture from 9 ulcers, and in mixtures in all but one of the remaining 15. If judged by the numbers of streptococci found in the portion of the ulcers sectioned, it is certain that the number of colonies obtained in the cultures did not represent the actual number present; either some were dead to begin with, or from long residence in the tissue failed to grow in the new environment, or many were killed in the sterilization of the surface. In

two cases of duodenal ulcer (one and twelve years old) in which the ulcers were so situated as to make their total removal impossible, the usual streptococcus was isolated from a thin layer of the inflamed peritoneum directly over the ulcer, and in one from the hyperemic parietal peritoneum directly opposite the ulcer (Cases 112, 134). In the former, diplococci were demonstrated in the tissue (Fig. 28). In the latter, this was not attempted. Non-hemolyzing staphylococci were isolated from 10 cases, but never in pure form. *Staphylococcus aureus* was found in one ulcer, but not in pure form (Case 902). *Bacillus Welchii*, in small numbers, was found in the ulcers or glands in 4 cases. They developed only in those tubes containing a large amount of the emulsion. A Gram-positive bacillus, probably belonging to the *subtilis* group, was found in 6 cases, and a large, unidentified, Gram-negative bacillus in 3. The colon bacillus was found in rather large numbers in 2 cases after death, and in small numbers in a duodenal ulcer in one case during life. Yeast-cells were isolated in large numbers from 3 ulcers, and in small numbers from 1. A few sarcinae were grown in one case, and diphtheroid bacilli in 3 cases.

TABLE 1.—SUMMARY OF FACTS AND RESULTS OF CULTURES IN GASTRODUODENAL ULCER

CASE	SEX AND AGE	PROBABLE AGE OF ULCER	LOCATION AND CHARACTER OF ULCER	RESULT OF CULTURES
1.	F., 25	3 years	Puckered ulcer of duodenum 2 cm. from the pylorus (0.5 x 0.6 cm.).	100 colonies of streptococci; a few staphylococci.
2.	F., 40	10 years	Constricted ulcer, anterior superior wall, 2 cm. above pyloric ring, 0.5 cm. in diameter, with clean base and infiltrated margin.	A few colonies of large, Gram-staining bacilli and staphylococci, and 280 colonies of streptococci.
B..	F., 28	5 years	Ulcer of stomach causing hour-glass constriction.	Moderate number of streptococci and staphylococci.
D..	M., 41	15 years	Indurated, puckered, deep ulcer of pyloric ring.	Many colonies of yeast, Gram-negative bacilli, streptococci, and staphylococci.
E..	Indurated ulcer of stomach.	Streptococci and a few staphylococci, and a large Gram-negative bacillus.
F..	F., 26	6 weeks	Ulcer of duodenum 2 cm. beyond pyloric ring.	200 colonies of streptococci; a few colonies of staphylococci and saprophytic bacilli.
J..	M., 54	6 years	Indurated ulcers in stomach and duodenum.	Pure culture of streptococci.
23 99.	Indurated ulcer of pylorus.	Streptococci, staphylococci, and large number of colon bacilli (cultures made after death.)
773..	M., 53	3 years	Indurated duodenal ulcer adherent to gall-bladder.	1500 colonies of staphylococci and 20 colonies of streptococci.
779..	F., 43	12 years	Indurated healing ulcer of duodenum.	180 colonies of staphylococci; 8 colonies of streptococci.

TABLE 1.—SUMMARY OF FACTS AND RESULTS OF CULTURE IN GASTRODUODENAL ULCER.—(Continued)

CASE	SEX AND AGE	PROBABLE AGE OF ULCER	LOCATION AND CHARACTER OF ULCER	RESULT OF CULTURES
849.	M., 26	7 years	Indurated ulcer of duodenum.	One colony of streptococci from gland draining ulcer.
860.	M., 50	..	A number of hard scars in pylorus and duodenum. Indurated undermined ulcer of pylorus (1 x 0.6 cm.).	Pure culture of streptococci from depths of ulcer; gland sterile.
870.	M., 65	3 months	Large, markedly indurated ulcer, extending half way around pylorus	Staphylococci, streptococci, and a few colonies of <i>Bacillus Welchii</i> .
885.	..	3 weeks	Acute perforating ulcer of stomach.	5000 colonies of a distinct, green-producing streptococcus in pure culture.
886.	M., 46	..	Chronic ulcer of stomach.	Lymph-gland cultured: two colonies of streptococci and 10 of <i>Bacillus Welchii</i> .
893.	M., 47	12 years	Indurated ulcer of duodenum, (2.5 cm.), perforated into head of pancreas.	2000 colonies of yeast, and a few sarcinae and streptococci from ulcer; from gland streptococci only; adjacent normal mucous membrane sterile.
902.	M., 51	4 years	Very large, markedly indurated, crater-like ulcer of pylorus (2 x 2.5 cm.).	340 colonies streptococci; 120 colonies <i>Staphylococcus aureus</i> , and 50 colonies of a diphtheroid bacillus.
904.	F., 20	A few days	Small, numerous, punctate ulcers of stomach, chiefly of fundus.	Large number of green-producing streptococci with marked involution forms, a few staphylococci, and colon bacilli (cultures made six hours after death).
909.	F., 42	..	Ulcer of stomach.	Cultures of gland from pylorus remained sterile.
947.	..	6 months	Adherent ulcer of duodenum.	Gland shows approximately 4200 colonies of green-producing streptococci in pure culture.
31.	F.	Many years	Markedly indurated ulcer of pylorus, margin abrupt, hard, and crater-like (3 x 2.5 cm.).	<i>Streptococcus viridans</i> , Gram-positive and negative bacilli, and staphylococci from floor of ulcer; streptococci from depths of indurated wall and from adjacent lymph-gland.
52.	F., 62	10 days	Five ulcers, three in the duodenum and two in pylorus.	6000 colonies streptococci, moderate number of colon bacilli, and a few staphylococci (culture made soon after death).
63.	..	Many years	Indurated ulcer of lesser curvature.	Gland cultured: spore-bearing bacilli, streptococci, and staphylococci.
69.	Indurated ulcer, posterior wall near lesser curvature.	From cultures from floor of ulcer, a few staphylococci; from emulsion of wall, two colonies of streptococci and Gram-staining bacilli.
82.	Large indurated ulcer of lesser curvature.	Cultures from two glands negative.
83.	M., 69	11 years	Ulcer of duodenum perforating into pancreas.	Cultures from gland negative.
104.	M., 54	10 years	Large ulcers, one of lesser curvature and one of duodenum.	From duodenal ulcer, a few colonies of colon bacilli, <i>Bacillus Welchii</i> , staphylococci, and streptococci. From gastric ulcer, large number of yeast colonies in upper portion of tube.
112.	F., 51	1 year	Subacute ulcer of duodenum; visceral and parietal peritoneum markedly congested.	From parietal peritoneum, five colonies of streptococci; from visceral peritoneum directly over ulcer, moderate number of streptococci and a few colonies of slender, Gram-staining bacilli.
120.	M., 55	7 years	Ulcer of duodenum just beyond pylorus, involving almost entire circumference.	Gland gave 18 colonies of streptococci.
126.	M., 20	10 years	Ulcer of duodenum 2 cm. beyond pyloric ring with recent perforation.	Gland gave pure culture of streptococci.
134.	M., 29	12 years	Duodenal ulcer just beyond pylorus.	Peritoneum directly over ulcer gave pure culture streptococci.

The results of the cultures in the broth were usually the same as those in the agar, although in some instances the former were positive when the latter were negative. The anaërobic cultures on blood-agar and Loeffler's serum slants were nearly always sterile. A number of times marked odor-producing bacilli were isolated, but these were not identified.

Lymph-glands, varying in size from 0.5 to 1.5 cm. in diameter, draining the ulcers, were cultured in 11 cases. Of these, 5 appeared to be sterile, 4 yielded streptococci in pure culture, 2 streptococci together with a few colonies of *Bacillus Welchii*. Colon bacilli were not found in any of the glands. The glands which proved sterile were all from cases of ulcer of long standing in which no exacerbation of symptoms occurred shortly before surgical intervention.

Both the ulcer and the adjacent lymph-glands were cultured in two cases (89 and 31). The glands in both yielded pure cultures of streptococci: the ulcer in Case 89 gave these together with yeast and sarcinæ; in Case 31 the ulcer gave *Streptococcus viridans*, Gram-positive and negative bacilli, and staphylococci from the floor of the ulcer, while the emulsion of the wall showed the same streptococcus as the lymph-gland in pure culture.

Cultures from the material aspirated from the floor of the ulcers were made in 10 instances, and from the emulsions of the adjacent normal gastric wall in 6. Four of the former and 3 of the latter proved entirely sterile. In 5 of the former and in 1 of the latter yeast-cells and sarcinæ were found in large or small numbers. These always grew only under strictly aerobic conditions, especially in the upper one-third of the tubes of dextrose agar. A few colonies of staphylococci were found in six of the cultures from material from the floor of the ulcer, and in one of those from emulsions of the gastric wall, and a few colonies of a large, Gram-positive, aerobic bacillus in four of the former. Hemolytic and green-producing streptococci developed in small numbers from the material from the floor of the ulcer in three instances, while from the normal gastric wall streptococci did not develop in a single instance.

Altogether, a more or less thorough search for bacteria in stained sections was made in 27 ulcers of the stomach and 20 ulcers of the duodenum. In 15 of the gastric and 10 of the duodenal ulcers cultures were made; the rest had been preserved in 10 per cent. formalin for from two to five years in the museum of the Mayo Clinic. Sections from all ulcers were stained with hematoxylin and eosin. Diplococci or short chains of streptococci were found

in the depths of the wall in 21 of the ulcers from the stomach (Figs. 29, 30, 31, and 34), and 15 of those from the duodenum (Figs.

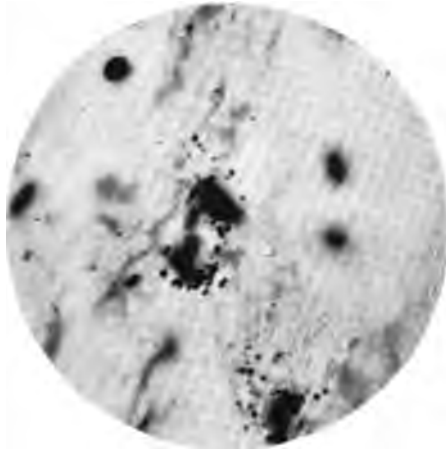


Fig. 29.—Streptococci and leukocytic infiltration in peritoneal coat in perforating ulcer of stomach in man ($\times 1200$).



Fig. 30.—Streptococci and leukocytic infiltration in peritoneal coat in acute ulcer of stomach in a woman sixty-two years of age ($\times 1200$).

32 and 33). It was found that the best place to search for the streptococci was near areas of leukocytic infiltration in the subperitoneum and along what appeared to be partition membranes or

lymph-channels. Yeast-cells were found in large numbers in three ulcers in the more or less dense connective tissue, and in small



Fig. 31.—Diplococcus in depths of scar tissue far away from ulcerated surface in an indurated ulcer of lesser curvature in a man fifty-six years of age. Ulcer present for five years; no exacerbation of symptoms shortly before operation ($\times 1200$).



Fig. 32.—Streptococci in depths of chronic three-year ulcer of duodenum in a woman forty-three years of age. No history of recent acute attack ($\times 1200$).

numbers in nine others of the ulcers of the stomach and in only three of those of the duodenum. In the one ulcer which showed

Staphylococcus aureus in the cultures, Gram-staining cocci were found in the depths of the tissue. No bacteria were found in the



Fig. 33.—Streptococci between mucous glands at the base of a chronic four-year ulcer of duodenum with acute symptoms for ten weeks before operation ($\times 1200$).



Fig. 34.—Streptococci and leukocytic infiltration in chronic ulcer with acute exacerbation shortly before operation ($\times 1200$).

adjacent normal mucous membrane in any case, and the floor of the ulcer only occasionally showed bacteria in the sections, and,

except in the ulcers excised after death, the number of these was small, consisting usually of large saprophytic bacilli, yeast-cells, and sarcinæ. In two of the lymph-glands a few Gram-staining diplococci were found in sections, both having yielded streptococci in cultures (Cases 120 and 126); while in one draining a duodenal ulcer of six months' duration (Case 947) the sections showed a rather large number of diplococci, and the portion cultured 4200 colonies of green-producing streptococci in pure culture. Cultures or sections have been made from ulcers or glands draining ulcers, altogether in 54 cases, and Gram-staining diplococci or streptococci have been demonstrated in 42 of these.

A study of the clinical history of the cases of ulcer in conjunction with the sections stained with hematoxylin and eosin and by Gram's method, and the results of the cultures from the lymph-glands draining ulcers and of the ulcer wall, show that the number of streptococci is greatest in the relatively acute ulcers and in chronic ulcers in which the clinical history and cellular infiltration indicate a recent lighting up of the infection, and fewest or even absent in the very chronic, markedly indurated ulcers with no clinical microscopic evidence of recent acute inflammation. Thus, in two cases of gastric ulcer in which yeast colonies were obtained in large numbers, showing their presence, when stained, in the depths of the tissue, in one of which a few streptococci were found and in the other none at all, the ulcers were markedly indurated, sections showed no recent cellular infiltration, and the clinical history no recent increase in symptoms—circumstances suggesting clearly that the ulcers had existed from ten to fifteen years. No such parallelism can be made out in the case of any of the other bacteria.

The results show that the bacterial flora of ulcers excised at operation is very much simpler than that of ulcers excised after death. The number and kinds of bacteria are relatively few, so that, contrary to the view generally held, reliable bacteriologic examination of gastric and duodenal ulcers in man can be made if proper methods are employed.

The cultural and other properties of the strains of streptococci isolated, particularly their pathogenicity, are reserved for a later

paper. It is sufficient here to state that the strains from 27 cases—all from chronic ulcers—produced small, moist, non-adherent, discrete, grayish-brown or grayish-green colonies on blood (human)-agar plates, and produced relatively short chains and diplococci, and a diffuse turbidity with much acid in dextrose and ascites dextrose broth, and that, when injected into dogs, rabbits, and guinea-pigs, the strains, on isolation, showed a relatively low grade of virulence, but a marked tendency to localize in the mucous membrane of the stomach and duodenum, producing circumscribed areas of infection associated with hemorrhage and ulceration in a high percentage of the animals inoculated intravenously; that in three cases—all from relatively acute ulcers—streptococci were isolated which produced typical green colonies and usually long chains in dextrose broth, but also showed marked affinity for the mucous membrane of the stomach or duodenum. The streptococci from the ulcers did not show such preference for relatively anaërobic conditions in ascites dextrose broth as had those from rheumatism. The largest number of colonies were found usually in the upper one-half of the tube.

The apparently almost constant occurrence of streptococci in the depths of ulcer, occurring in man, commonly the more numerous the younger the ulcer and the more marked the cellular infiltration, to the total or almost total exclusion of other bacteria, and the fact that when injected into animals such streptococci show a marked tendency to localize in the stomach or duodenum, a property which other strains of bacteria isolated do not possess, taken in conjunction with clinical facts, constitute good evidence that the streptococci are not merely accidental secondary invaders of the tissues, but are commonly the original cause, as well as the important factor in preventing the healing of the ulcer.

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THE TROPHIC ELEMENT IN THE ORIGIN OF GASTRIC ULCER *

LUIGI DURANTE

It has been found that gastric ulcer can easily be produced by the following conditions:

1. By lesions of the central nervous system.
2. By lesions of the gastroduodenal nerves, *i. e.*, disturbing the innervation of—(a) The vagus cervicalis, thoracic subdiaphragmatic; (b) the sympathetic nervous system in the rami which communicates between the fifth and ninth dorsal vertebræ in the thoracic and subdiaphragmatic splanchnic nerves, in the solar plexus, and in the lumbar chain.
3. Through local circulatory disturbances by means of embolism.
4. Through ligation of the portal veins.
5. By removal of the adrenals.
6. By trauma of the epigastric region.
7. By direct trauma of the stomach.
8. By artificially produced hemoglobinemia.
9. By anemia produced by pyrocin.
10. By the ingestion of bacteria.
11. By intravenous injection of bacteria.
12. By intravenous injection of bacterial toxins.
13. By intravenous injection of mineral poisons and autolytic toxins.
14. By intravenous injection of adrenalin.
15. By injection of adrenalin into the wall of the stomach.

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16. By cutaneous burns.

17. By artificially produced insufficiency of the pylorus and ingestion of the trypsin.

The above methods have been used singly or in the following combinations: (1) Joint resection of the vagus and sympathetic nerves; (2) trauma and ingestion of 0.5 per cent. hydrochloric acid; (3) trauma and anemia produced by graduated bleeding; (4) trauma combined with bacterial infection; and (5) resection of the cervical spinal cord combined with injection of 0.5 per cent. hydrochloric acid.

It must be borne in mind that whereas some experiments yield positive findings, control experiments often give negative results. This has been especially true of the experiments dealing with the disturbance of the vagus or the sympathetic nervous system.

It will be readily understood that, with the extensive experimental material at their command, the defendants of any given theory could easily cite facts apparently proving their conception to be correct, while the opponents could as easily collect contradictory evidence. Hence no theory has gained general acceptance, since no conclusive evidence could be brought forward in any one single case. To make evidence conclusive, gastric ulcer has to be reproduced in animals.

As far as is compatible with the peculiar morphology of the species, the lesion created must be a destruction of tissue identical in animals as regards anatomic and pathologic structure, with acute and chronic ulcer in man.

The Pathogenetic Problem.—The lesion must occur under conditions similar to those needed for the formation of ulcer in man. Under normal conditions the vitality of the gastric mucosa is directly dependent on three factors: secretion, circulation, and innervation (the latter being the result of the two former) inasmuch as the secretory glands are stimulated by nerve impulses and food-supply through their innervation and blood-vessels. In order to obtain a "clean experiment," we must create a disturbance in one or more of these three fundamental factors, thus attacking the life of the cell at its very roots.

Secretion.—The pathogenetic value of the gastric juice (if the latter can be considered a cause of gastric lesions through autodigestion of the mucosa) is by no means clear. This may be the result of one-sided conceptions. Faulty clinical deductions, stating that gastric ulcer must be accompanied by and originate from hyperacidity, have suggested the following series of experiments: (a) Giving hydrochloric acid by mouth over a prolonged period; (b) the use of subcutaneous injections of hypertonic sodium chlorid solutions intended to increase the actual amount of hydrochloric acid in the gastric juice.

Only negative results were obtained by these methods, which were bound to result in failure, since the promise that quick digestion is the result of hyperacidity is itself based on misconception. If we are to accept the theory that destruction of tissue can be caused by autodigestion, more accurate knowledge of the actual chemical value possessed by each of the various components of the gastric juice should lead us to attribute these lesions of the mucosa either to an excessive production of peptic or to an insufficient quantity of antipeptic ferment.

Both hyperacidity and hypoacidity are met with in gastric ulcer, and should rationally be considered useful and natural measures of defense, counterbalancing the corroding effects of the pepsin, since Pawlow's experiment has proved that *in vivo* as well as *in vitro* the activity of pepsin is inhibited by both hyperacidity and hypoacidity.

If any influence on the course of gastric ulcer can be ascribed to the gastric juice,—and we may readily conceive that it cannot be entirely without effect, since gastric ulcers appear in that part of the digestive tract which is constantly brought into contact with the gastric juice, or in places that have been artificially put under similar conditions (gastro-enterostomy),—we are logically bound to attribute this influence to the action of the gastric ferments whose chemical activity has not thus far been clearly demonstrated.

Circulation.—Among the experiments aiming at the reproduction of gastric ulcer through disturbed circulation, those blocking

the minor vessels of the gastric mucosa by means of embolism have given the most satisfactory results. No results have been obtained by obstruction of the larger gastric and duodenal vessels. The following explanation seems admissible for the phenomenon: the larger vessel can reestablish a sufficient circulation by means of collaterals; the small vessels, on the contrary, though they cannot be called "terminal" in the true anatomic sense, are in reality "terminal" from a functional point of view, and are incapable of supplying a sufficient collateral circulation.

The formation of gastric ulcer on the basis of embolic obstruction in the minor vessels of the gastric mucosa has proved conclusively that a disturbance of circulation in these vessels is in itself sufficient to produce typical circumscribed necrosis of the mucous membrane; the necrotic area thus formed is conic in shape, its base being nearest the surface, and presenting, after removal of the slough, the true picture of gastric ulcer. Ulcers thus produced are, as shown by the initial lesion and by their subsequent development, an exact replica of acute, not chronic, ulcer in man. They end in the formation of a scar with a complete regeneration of the mucosa (at least in such animals as survive operation for a sufficiently long period). Every attempt at thus reproducing chronic ulcer has resulted in failure. If, as has been shown, the pathogenesis of acute ulcer may be explained by circulatory disturbances of embolic origin, this explanation has proved inadequate to solve the problem of the origin of chronic gastric ulcer.

Innervation.—Physiology has not yet clearly established what phenomena in the various phases of gastric motility and secretion are to be attributed to the influence of the vagus or the sympathetic nerves respectively. This is probably due to the fact that both systems of innervation are so intimately associated—by their anatomic features as well as by their functional activity—that it is practically impossible to stimulate the one system by itself and prevent the action of the stimulus from being transmitted to the other.

Recent investigations have shown that both systems of innervation are equally involved in the regulation of secretion and mo-

tility, both exerting an exciting and restraining influence at the same time.

The sympathetic nerve, moreover, apart from the functions in which it coöperates with the vagus, also controls the circulation of the vasomotor nerves of the stomach, and carries impulses of profound sensibility to the central nervous system. Owing to the part which the sympathetic nerve plays in the nutrition of the gastric mucosa, by regulating its circulation the title of "trophic nerve" is applicable to it in the most liberal sense.

As has already been stated, attempts to reproduce gastric ulcer by means of disturbed innervation result in a great diversity of findings; and if positive and negative results cannot actually be said to contradict each other, at least the latter contain many new suggestions for the unraveling of the problems in question.

Although lesions presenting all the anatomic features of acute ulcer in man could be produced, it did not seem possible to obtain the true chronic form. The only description of artificial ulcers, presenting anatomic features of chronicity and produced by disturbed innervation, may be found in Dalla Vedova's² monograph; these were obtained either by injecting alcohol into the splanchnic nerves, or by resecting these nerves after laparotomy.

*Personal Findings.*³—Dalla Vedova's method suggests the following criticism: Ulcers forming after a laparotomy has been done cannot be said to be the direct result of nerve-resection only, as the manipulations needed to reach the nerves are bound to disturb and damage the surrounding viscera. It need hardly be emphasized that the operative technic is of primary importance in experiments of this kind, but even with faultless technic the fact remains that lesions which, under normal conditions of circulation and innervation, might be of little consequence, are bound to give rise to severe complication when the nerves themselves have been tampered with. To defend my experiments against these very valid objections, I have chosen the lumbar route for operation, and attacked the splanchnic nerves extraperitoneally with one incision in the middle space of the costovertebral angle. This method, though by no means easy, excludes all damage to the viscera, and

also enables one to resect the large, the median, or the small splanchnic nerve individually. I have used dogs and rabbits for my experiments, with a view to comparing the results to be obtained in animals presenting different types of morphologic evolution and dependent on a different diet for nutrition.

The following results were obtained after resection (75 experiments) of the right and left splanchnic nerves:

1. Neither subsequent hemorrhagic nor necrotic lesions were found to occur after resection of the major splanchnic nerve during a period of observation lasting from one to one hundred and twenty-five days. Immediately after operation, however, signs of congestion might be seen in the gastric mucosa which cleared up in about ten or twelve days. Slight atrophy of the gastric cells, more particularly of the zymogenic cells, remained.

2. Resection, or ligation by means of silk thread, of the median splanchnic nerve invariably caused numerous circumscribed hemorrhagic lesions side by side with non-hemorrhagic lesions, presenting the characteristics of simple necrotic degeneration. These lesions we have found in the "cardiac pouch" in rabbits and in the pyloric region in dogs. Hemorrhagic lesions of the pylorus and duodenum are rare in rabbits, while duodenal lesions are rare in dogs.

3. Resection of the minor splanchnic nerve occasionally resulted in slight hemorrhagic lesions in the above-mentioned regions.

4. Simultaneous resection of both median and minor splanchnics caused lesions identical with those already mentioned.

5. Combined resection of the three splanchnic nerves produced lesions identical with those described for the median branch, only more pronounced in character.

6. Whenever the median splanchnic nerve alone was resected or ligated, signs of hemorrhage and intense congestion of all the blood-vessels were seen in the adrenal of the corresponding side in both medulla and cortex; but those changes did not occur if the major splanchnic nerve alone was resected.

Macroscopically, the hemorrhagic lesions produced by resection of the median splanchnic nerve have the appearance of small

dark specks which are sometimes grouped together so as to form circular hemorrhagic areas from 5 to 10 mm. in diameter. These areas may be seen a few hours after operation (Fig. 35). In the various stages of their development the initial lesion appears to be due to a minute lesion in a blood-vessel of the muscularis mucosæ; from this point the hemorrhage spreads, infiltrating and destroying the mucosa. The hemorrhagic area becomes conic in



Fig. 35.—Rabbit's stomach six hours after resection of left middle splanchnic nerve. Extensive hemorrhagic condition of mucous membrane.

shape, its base coincident with the surface of the mucous membrane (Fig. 36).

Sometimes the force with which the hemorrhage starts is so great that its mere mechanical action suffices to rupture all the layers of the gastric mucosa, as seen in the stomach of a rabbit which died about six hours after operation (Fig. 37). The two varieties of hemorrhagic lesion, *i. e.*, hemorrhagic specks and groups of these, heal without any apparent connective-tissue reaction, through regeneration of the gastric mucous epithelium, the latter

growing down along the edges of the ulcers and lining the cavities (Fig. 38).

In lesions resulting from direct injury to the mucosa healing is far more rapid. In these hemorrhagic lesions the ulcerous cavity is not completely covered by epithelium even twenty-five days after operation. This seems to justify the conclusion that dis-

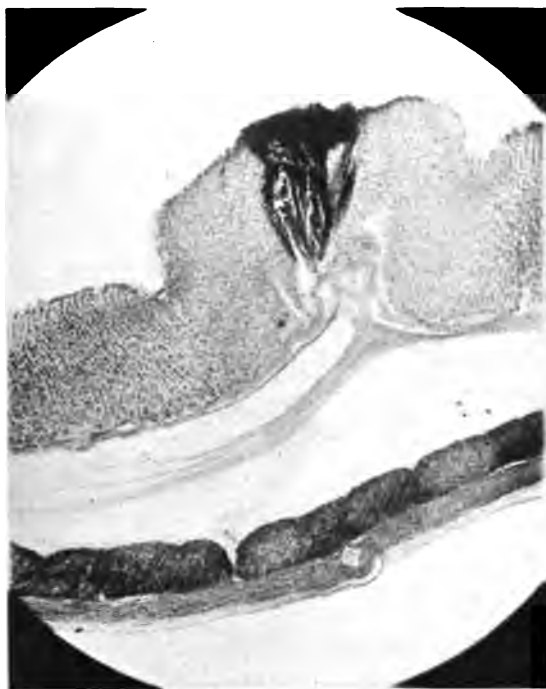


Fig. 36.—Hemorrhagic lesion of mucous membrane from blood-vessels of muscularis mucosae. Rabbit's stomach two hours after resection of left small splanchnic nerves ($\times 60$). Hematoxylin-eosin stain.

turbed innervation not only causes circumscribed hemorrhages, but also results in a slight alteration of the entire mucosa. Careful observation reveals the histologic features to consist in a slight degree of atrophy of all the cells, especially of the zymogenic cells, and a certain amount of distortion in the formation of gastric glands. This points to a process of retarded regeneration.

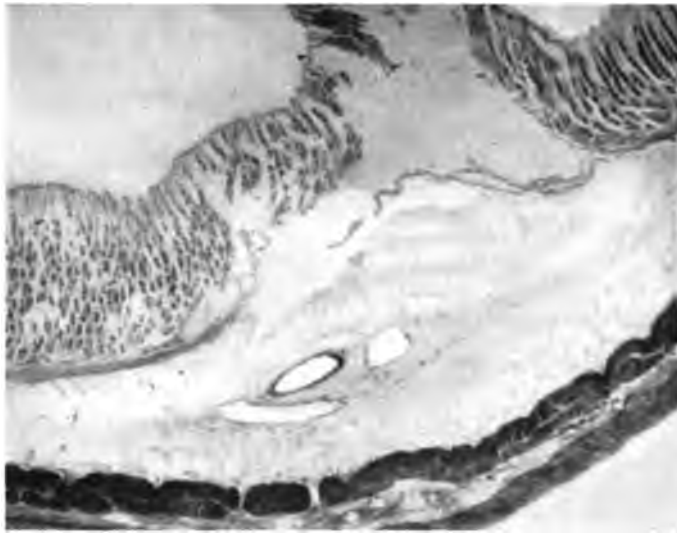


Fig. 37.—Hemorrhagic lesion from violent rupture of the blood-vessels of the muscularis mucosae and destruction of the mucous membrane. Rabbit's stomach six hours after resection of right and middle splanchnic nerves ($\times 60$). Bensley's stain for zymogen granules.



Fig. 38.—Spastic condition of the blood-vessels of muscularis mucosae. Incipient necrotic area in the mucous membrane. Rabbit's stomach six hours after resection of left middle splanchnic nerve ($\times 60$). Bensley's zymogenic stain.

As stated above, necrotic areas, as well as hemorrhagic lesions, are found in these experiments. The former are few in number, and show macroscopically as small, round, pale areas. Their lack of color causes them to stand out sharply against the congested mucosa. Serial sections show these necrotic areas to have exactly the same shape as the hemorrhagic lesions already described (Fig. 39). They do not, however, contain the slightest vascular lesion nor show any sign of extravasation. Careful study of their subse-

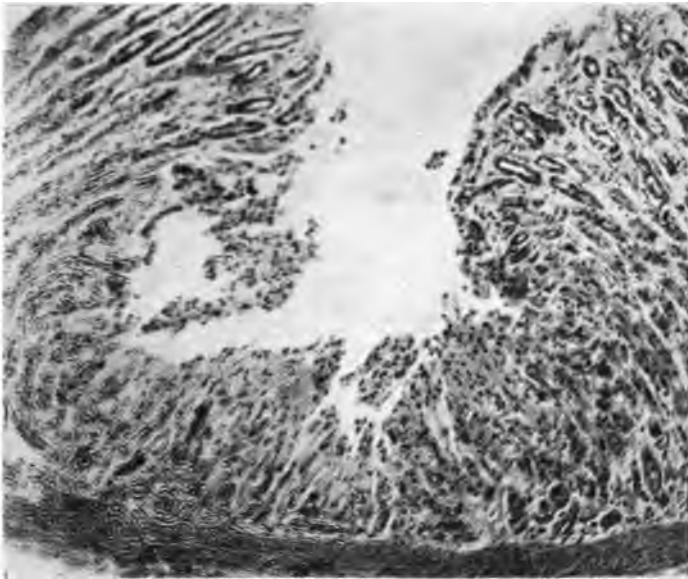


Fig. 39.—Ulcer, healing by proliferation of surface mucous cells. Rabbit's stomach twenty-five days after resection of all right splanchnic nerves ($\times 130$). Mucin stain.

quent course has led me to believe that they are the first stage of a specific kind of ulcer which I am about to describe, and which presents all the characteristic features of true chronicity.

The gradual development and terminal stages of these ulcers can be traced with great accuracy in experiments on dogs. The accompanying photomicrographs (Figs. 40 and 41) show two ulcers taken from the pyloric region of the same dog which died thirty-



Fig. 40.—Small typical callous ulcer in the pyloric region. Both edges are composed of young proliferating connective tissue. No trace of epithelial regeneration. Dog's stomach thirty-five days after resection of all the three left splanchnic nerves ($\times 60$). Weigert-van Gieson stain.

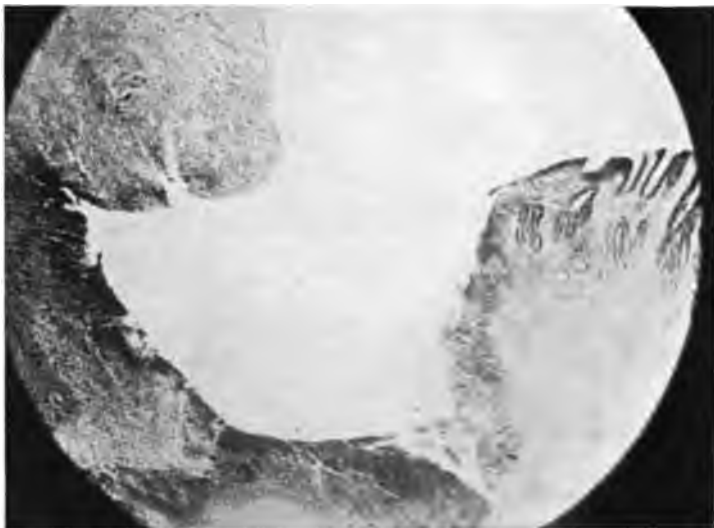


Fig. 41.—Large callous ulcer in the pyloric region of same specimen as Fig. 37 ($\times 70$). Safranin stain.

five days after resection of the three left splanchnic nerves. The lesions involve the mucosa and submucosa as far down as the muscular stratum; they show signs of infiltration and necrosis; no trace of epithelial regeneration can be found; the edges are covered with young connective tissue. Besides these ulcers, other lesions may be seen in the pyloric region, the latter all completely healed through a process of complete epithelialization. In these no connective-tissue reaction whatever can be observed. The results obtained offer the following points of discussion:

1. *Character of the Ulcer.*—As has been seen, disturbed innervation alone, without any additional trauma or infection, will suffice to create in animals lesions presenting all the essential characteristics of acute and chronic ulcer in man. These results are, of course, comparable only as far as their morphologic and histologic similarity is concerned. Clinical observations must need be valueless in dealing with different species. Comparison is made further impossible by the fact that animals survive these operations for a short time only, and the lesions, being very extensive, are likely to be complicated by changes of metabolism. As we find chronic and acute ulcers in the same region of the same stomach, both originating at the same time, there is reason to assume that time does not play a paramount part in the process; *i. e.*, that acute lesions do not take on chronic form, but that both varieties occur simultaneously and start as specific entities. Moreover, as both small and large chronic ulcers will be found in the same stomach, it is apparent that the size of the ulcer cannot be responsible for its insufficient healing.

2. *The Origin of the Ulcer.*—A systematic study of the results obtained after resection of each splanchnic branch by itself seems to indicate that these nerves do not play identical parts in preserving the integrity of the mucous membrane. Resection of the major splanchnic nerve, although causing temporary paralysis of the gastric vessels, is not in itself sufficient to produce permanently destructive lesions. The lesions obtained can only be compared with those resulting from resection of the median nerve. At first sight this diversity of action seems contradictory;

it is explained by the different degree in which the two nerves influence the blood-pressure. It has shown that more telling effects may be obtained by stimulating the median splanchnic nerve than are seen after stimulation of the large splanchnic nerve, even though the latter control the larger field in abdominal circulation, faradic stimulation being used in both cases. This apparent contradiction is easily explained by the fact that the median splanchnic innervates the adrenals; stimulation results in an increased secretion of adrenalin, and, as the adrenal secretion has a physiologic as well as a selective action, it is one of the most powerful means by which contraction of blood-vessels can be produced. The results which I have obtained after resection of the median splanchnic nerve only seem to illustrate the influence of this nerve on the adrenals, both by the rapidity (few hours after the lesion) with which the lesions appear and on account of the hemorrhages by which they are accompanied. Overstimulation, rather than insufficient innervation, seems to be the principal cause, for it must be remembered that intravenous injection of adrenalin has proved conclusively that, by increasing the adrenalin content of the blood, hemorrhage can be produced in the gastric mucosa.

3. *The Non-hemorrhagic Lesion.*—To what cause are we to attribute the formation of the other, non-hemorrhagic lesions? It does not seem logical to assume that they are due merely to circumscribed trophic disturbances: if this were the case, they ought to be found principally after resection of the major splanchnic nerve, and they are not. The following explanation seems to me admissible: namely, that we are dealing with spastic disturbances, due to the action of adrenalin, and that whereas this action causes rupture of the blood-vessel in some points, it leads only to spastic contraction in others. Klebs has already proved himself a warm defendant of the idea of "vascular spasm," which, however correct it may be, is unfortunately beyond conclusive proof, as it cannot be made visible. By its very nature spastic contraction of a small blood-vessel remains a functional disturbance and does not leave visible traces on the arterial wall.

SUMMARY

1. The peripheral innervation of the stomach can be said to be "trophic" in its action, as it regulates circulation and stimulates secretion, besides transmitting impulses of profound sensibility.

2. Insufficient innervation of the gastric mucosa can be traced only after some time by a slight atrophy of gastric cells. This fact may be explained by congestion and by a deficit in secretory impulses, as the latter, in accordance with the laws of biology, are known to act as stimuli of nutrition and growth.

3. Trophic disturbances are not in themselves sufficient to cause ulceration unless accompanied by vascular disturbances resulting in hemorrhage or spastic contraction of the vessels.

4. Ulcers produced by resection of the vagus cannot be explained if we do not take into account the vasomotor disturbance by which they are accompanied. If the vasomotor disturbances accompanying them are duly taken into account, they may readily be explained by the transmission of nervous impulses to the sympathetic fibers contained in the vagus, and by the numerous anastomoses existing between the two nerves which cause the stimulus to be transmitted from one nerve to the other.

5. Acute and chronic ulcers produced by resection of the splanchnic nerves develop with great rapidity; this is due to the fact that the operation irritates the nerves of the adrenal medulla, in consequence of which greater quantities of adrenalin are forthwith secreted. The adrenal secretion stimulates the sympathetic nerve-fibers, controlling the non-striated muscles of the blood-vessels, thereby causing the formation of hemorrhagic and spastic lesions. Whereas the hemorrhagic lesion, presenting the essential features of acute ulcer, heals by means of a scar, the spastic lesion becomes the starting-point of genuine chronic ulcers.

6. Symptoms of deficient innervation appear only after specific characteristics of both types of ulceration are fully developed. Consequently nervous disturbances cannot be considered the primary cause of gastric ulcer, although it must be admitted that

disturbed innervation plays some part in the subsequent development of the ulcers.

7. By resection of the splanchnic nerves ulcers may be produced in animals, of which the histologic picture contains all the essential features of acute and chronic gastric ulcer in man.

THE ETIOGENETIC PROBLEM

Having reviewed the pathogenetic features of gastric ulcer and the numerous theories brought forward to explain them, the question remains to be discussed: Whether experimental work can be said to have furnished new suggestions corroborating or refuting the various conceptions of the etiology. It does not seem logical to assume that gastric ulcer should be caused by a single etiologic factor only, since we find it to be associated with the most widely divergent clinical syndromes, with symptoms of melæna neonatorum in infants, with trauma of the epigastric region, nephritis and uremia, burns, sepsis, toxemia, oligemia, bacterial infections, incarcerated hernia, tabes, malaria, tuberculosis, and lues. In the majority of cases, however, ulcers appear spontaneously; no apparent relation to other diseases can be traced. This type of ulcer, which exhibits all the most typical features of the disease, presents the greatest problems to scientific investigation; its etiology is of paramount importance. On the edges of some of these ulcers which had all the characteristics of true chronicity, and for whose formation neither clinical nor anatomic causes could be found, colonies of bacteria were discovered by Boettcher. The hypothesis contending that gastric ulcer is produced by the cytolytic local activity of bacterial toxin is based upon this observation. Other explanations of the fact seem, however, equally admissible; the presence of bacteria may as logically be considered the result as the cause of gastric ulcer, and the contention seems justifiable that the presence of bacteria in the wall of the stomach is merely an evidence of subsequent infection, since disturbed nutrition itself creates lessened resistance. Experimental work was brought to bear upon the question. Attempts were made to produce ulcer by feeding animals with both toxins and bacteria. The

lesions thus created did not in any single instance possess the characteristic features of acute or chronic ulcer in man; the ulcers produced appeared to be mere foci of infection starting in the lymph-follicles of the gastric mucosa. Rosenow⁴ alone succeeded by repeated inoculation in reproducing ulcers of the genuine human type by streptococci from ulcer in man.

If the results obtained in experimental work do not exclude the possibility, from an etiologic point of view, of ulcers forming in consequence of bacterial infection (as the clinical observation of Boettcher and the experimental work of Rosenow seem to indicate), the fact remains none the less that bacteria are found in a limited number of cases only.

Owing to the important part played by nervous disturbances in the experimental formation of gastric lesions, they are entitled to a place among the morbid causes. The nervous disturbances may be central or peripheric. I have mentioned the central factor because, as is well known, excessive psychic stimuli are capable of so changing the normal vasomotor tonus that vascular disturbances culminating in rupture of the small arterial walls may be caused in any part of the body—a fact which may be explained by the close association, both in anatomy and function, of the sympathetic nervous system and the cerebrospinal tract.

The peripheral or anatomic factor must be taken into especial account, since toxic stimuli—whether due to bacterial, to chemical, or to biochemical agents—are capable of producing irritations in the sympathetic system, entirely comparable with those I obtained by means of surgical interference. *In other words, ulcer may be produced by any agent capable of damaging the sympathetic nervous system, as it is on the integrity of this system, which controls circulation, secretion, and profound sensibility in the stomach, that the very life of the gastric cell may be said to depend. The theory of "trophic ulcer" must be taken in this sense.*

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A STUDY OF THE GASTRIC ULCERS FOLLOWING REMOVAL OF THE ADRENALS *

FRANK C. MANN

It was noted at autopsy that animals dying after the removal of both adrenals showed acute ulceration of the gastric mucosa in a large number of cases.

Cioffi¹ and Pende² made this same observation, but Gibelli³ was the first to give it special attention. The most extensive investigation of the subject was made by Finzi⁴ in a study of the gastric mucosa of rabbits and dogs after removal of the adrenals. He found in the gastric mucosa marked circulatory changes consisting of edema, hemorrhage, necrosis, and ulceration. In the few instances in which there was a tendency to heal, the slight healing process involved only the connective tissue, never the epithelium. He found edema and hemorrhagic points in the stomach as early as one hour after extirpation of the adrenals. Dissection of the capsule of the adrenal, leaving the gland intact, did not produce ulceration. The removal of one adrenal in a rabbit produced slight and transient circulatory changes in the gastric mucosa. Animals which were given adrenalin after removal of the adrenals had normal gastric mucosa. In five cases of gastric or duodenal ulcer in man he found microscopic changes in the adrenals, consisting of thickening of the capsule, nodular hypertrophy, fatty degeneration, great congestion, and multiple hemorrhage. He believes that adrenal insufficiency may be a factor in the etiology of gastric ulcer.

Durante⁵ investigated the effects of section of the splanchnic

* Received for publication, November 15, 1915. Reprinted from *Jour. Exper. Med.*, 1916, xxiii, 203-210.

nerves on the gastric mucosa and adrenals in dogs and rabbits. He found that section of all three splanchnics on either side produced no change except congestion in the adrenals; section of the major splanchnic affected the gastric mucosa very slightly; section of either the median or minor splanchnic on either side always produced necrosis and ulceration of the gastric mucosa. The ulcers produced by section of the nerves on the right always healed rapidly and the spleen remained normal; section of the nerves on the left produced changes in the spleen and ulcers in the stomach which tended to become chronic. He attributed the formation of ulcers after adrenalectomy to incidental injury of the minor splanchnic nerves which are buried in the posterior edge of the adrenal.

Since this investigation was undertaken two articles bearing on the subject have appeared. Elliott⁶ notes the frequent occurrence of gastric ulcer on removal of the adrenals in cats, and cites it as proof of the full digestive power of the gastric juice. He refers to the work of Finzi and concludes with the statement that gastric ulcer is not found in Addison's disease.

Friedman⁷ investigated the effect on the gastric and duodenal mucosa of removal of the adrenals and one-sided thyroidectomy in dogs and rabbits. He considered gastric lesions possibly dependent on adrenal insufficiency as well as on an excess of thyroid; duodenal lesions on hypofunction, as well as upon excess of adrenalin; coexistent gastric and duodenal lesions on alternating conditions of hypofunction and hyperfunction of the adrenals. He relies on the pluriglandular hypothesis of an antagonistic action between the adrenals and the thyroid to explain the formation of gastric and duodenal ulcers and erosions after interference with these glands.

Dogs and cats were used in my investigation.* As no lesion of the gastric mucosa was found at autopsy in a series of more than 200 practically normal animals, it would seem that spontaneous ulcers are not common in these animals. Their occurrence after adrenalectomy was studied in the following series of experiments.

* These ulcers have also been noted in gophers dying from adrenal insufficiency, and in one case of Addison's disease.

Experiment 1.—In four dogs the adrenals were removed at one operation and the animals kept under an anesthetic until death occurred, two or three hours after the removal of the last gland. In these experiments the mucosa of the stomach and duodenum was found to be normal.

Experiment 2.—In 12 dogs the adrenals were removed at two operations. When the second gland was removed, the dogs were kept under ether until death occurred, which was from two to eight hours after operation. In none of these animals were gastric or duodenal lesions noted.

Experiment 3.—Forty dogs and six cats were subjected to the removal of one adrenal, usually the right, and killed at periods varying from five hours to two hundred and thirty-five days after operation. In this series of animals no lesion of the gastric or duodenal mucosa was found except in one dog. This animal died from an unknown cause four months after removal of the right adrenal; several acute ulcers and one chronic ulcer were found in the stomach and one acute ulcer in the duodenum.

Experiment 4.—Of 60 dogs and 5 cats in which both adrenals were removed at the same operation or at different operations, 40 animals showed lesions of the stomach, 5 of these ulcers of both stomach and duodenum. Of the 25 animals in which ulcers were not found, only 4 died an uncomplicated death from adrenal insufficiency; the remaining 21 animals were either subjected to other experiments which may have interfered with the formation of ulcers or they died before the ulcer could form.

It is seen that lesions of the gastric and duodenal mucosa did not occur in adrenalectomized animals subject to continuous etherization, and were infrequent in animals subjected to the removal of only one adrenal; but lesions in the stomach and duodenum occurred in about 90 per cent. of the animals dying with the characteristic symptoms of adrenal insufficiency after removal of both glands. This last fact appears significant in the study of the general causative factors of acute gastric ulcers.

It has been impossible to determine definitely the time necessary for the formation of the ulcers or how soon after complete adrenalectomy they begin to form. In only one of the animals examined within ten hours after removal of both adrenals were any

changes noted in the gastric mucosa. In this instance there were several hemorrhagic areas which were possibly the beginning of ulcers. In one animal dying twenty-two hours after extirpation of both glands well-formed ulcers were present. In animals examined when muscular weakness was first in evidence, beginning ulceration was noted. No changes in the gastric mucosa were found before decrease in blood-pressure took place. It would appear that ulcer formation begins before the onset of the characteristic symptoms of adrenal insufficiency which progress until the death of the animal, and that only a few hours are necessary for their production.

The lesions found in the gastric mucosa after death from adrenal insufficiency consist of two main types: one is a wide-spread, superficial erosion; the other is a true, punched-out ulcer formation.

The gastric erosions practically always occurred in the fundic division, and in most cases the pyloric mucosa appeared normal. They appeared to begin in and spread along the rugæ, thus producing an irregular appearance. Only the surface of the mucosa was affected, the loss of epithelium never extending to the sub-mucosa. The denuded surface was hemorrhagic in appearance, and the fluid in the stomach was usually blood-stained. This condition developed mainly in those animals in which there was a prolonged moribund condition following the development of muscular weakness.

The gastric ulcers were round or oval in shape and varied in size from 2 mm. to 2 cm. in diameter. They were usually multiple, but a few stomachs contained only one ulcer. Their position varied; they were found in the fundic and pyloric regions on both the greater and lesser curvatures. Usually they occurred in the pre-pyloric division. Beginning ulcers appeared as small hemorrhagic areas; when fully formed, however, they penetrated to the muscularis mucosæ, with a complete loss of epithelium. The walls were smooth, giving the characteristic punched-out appearance. A small blood-vessel was usually found in the base of the ulcer. When the autopsy was performed immediately after death, in many instances the vessels were bleeding. In the pyloric region

the blood gave the ulcer a black appearance, while in the fundus it often remained bright red at the site of the ulcer. In most instances the ulcers constituted the only pathologic change in the mucosa, while in other specimens the mucosa was injected throughout (Figs. 42 and 43).

The duodenal mucosa was usually congested in the adrenalectomized animals. In five experiments there were definite ulcers.



Fig. 42.—Gastric mucosa of a dog, showing multiple acute ulcers.

These duodenal ulcers occurred just distal to the pyloric ring and appeared like cauterized areas about 1.5 cm. in diameter. They were deeper at the center than at the edges. They penetrated to the muscularis mucosæ at the center. They never showed evidence of hemorrhage (Fig. 43).

Microscopically, the picture of the ulcer varies slightly; usually,

however, they are cone-shaped, with the base of the cone at the surface and the apex at the muscularis mucosæ. The edges of the ulcer are clean, although occasionally there may be some cellular



Fig. 43.—Pyloric and duodenal mucosa, showing multiple acute ulcers.



Fig. 44.—The center of a gastric ulcer, showing the clean edges and base.

débris and blood at the base (Fig. 44). None but the earliest signs of healing have ever been observed.

The loss of tissue appears to begin at the surface. The gland-cells disappear first, allowing the supporting tissue to fall together. In some cases the ulcer has not extended to the muscularis mucosæ.

In these ulcers the gland-cells below the base may appear perfectly normal. Hemorrhage seems to be of early occurrence in the formation of the ulcer. In practically all ulcers the blood-vessels in the vicinity are congested. The special stains for mucin demonstrate the fact that this substance is usually absent near the ulcers (Fig. 45). The glands in the vicinity of the ulcer may appear normal, but do not contain mucin. The zymogen content of all the cells is decreased, but no more so in the cells around the ulcer than elsewhere.

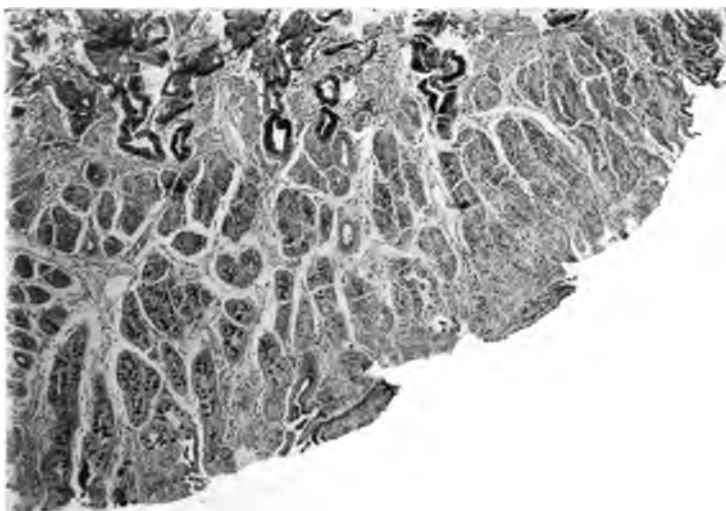


Fig. 45.—The edge of a duodenal ulcer, showing the loss of goblet-cells (the dark stained cells) in the vicinity of the ulcer.

It has been suggested that the regurgitation of pancreatic secretion is the cause of gastric ulcers and that tryptic ulcer would be a more exact term than peptic ulcer. That the pancreatic secretion is not necessary for the formation of these ulcers was proved by a series of five experiments in which the pancreatic ducts were either doubly ligated and sectioned, or a pancreatic fistula was made before the removal of the last adrenal. In these animals no pancreatic secretion could reach the gastro-intestinal tract, yet many characteristic gastric ulcers were found after death.

It has been demonstrated that bile in association with a strongly acid gastric juice has an erosive action on the gastric mucosa.⁸ That the bile might be of importance in the production of these ulcers seemed possible because of the fact that the fluid found in the stomach was usually bile-stained. In one animal the common bile-duct was transplanted to the skin, thus making it impossible for any bile to enter the stomach. After complete recovery from the operation, the adrenals were removed. Well-formed ulcers were found at autopsy.

The gastric content was always acid in the adrenalectomized animals. In order to determine the part the acid played in the production of the ulcers, an attempt was made to neutralize it during the moribund period. To accomplish this sodium bicarbonate was administered about every four hours, either in solution by stomach-tube or in capsules. Of course, it was impossible to be sure that the gastric contents were always kept neutralized, but certainly in most instances no great excess of acidity developed. In a series of ten experiments in which sodium bicarbonate was administered after the removal of the last adrenal, ulcers were found in one animal only. In this experiment it is possible that the bicarbonate was not given frequently enough to prevent the development of acidity. This result would tend to show, as has been demonstrated in regard to the formation of other acute ulcers, that acid is a factor in their production.⁹

In a series of ten experiments a gastro-enterostomy was performed during the interval between the removal of the adrenals. In only four of these animals were ulcers found. It is possible to explain this result as due to a reflux of the alkaline intestinal secretion and the bile.

SUMMARY

Acute ulcers of the gastric mucosa are found in a large percentage of dogs and cats dying after adrenalectomy. These ulcers seem to develop during the moribund period. They are apparently peptic ulcers forming at the site of local hemorrhages in the gastric mucosa. They are true acute ulcers, usually penetrating to the muscularis mucosæ with a total loss of epithelium. They

develop in the absence of pancreatic secretion and bile. However, they appear to develop only in an acid medium.

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THE ROENTGENOLOGIC DETERMINATION OF GASTRIC MOTILITY

With a Comparison of the Results Obtained in a Series
of Cases Examined by Both the Roentgen
Ray and the Test-meal *

RUSSELL D. CARMAN AND ALBERT MILLER

The testing of gastric motility by roentgenologic methods has been of such striking and practical value that it seems worth while to report the results obtained in a considerable series of patients operated on and to compare them with the findings gained by the test-meal and stomach-tube. We have subjected approximately 10,000 patients to the roentgen test, but have selected for tabular analysis and comparison those patients seen during the year 1914. In 1914, 4118 patients were examined by the roentgen ray for gastrointestinal disease. Of this number, 1140 were operated on. In 950 of them a motor-meal test was also made by the gastro-enterologist, and the tabulation is based on these 950 cases.

Before discussing the results it may be well to recall some of the elementary facts as to the physiology and pathology of the gastric motor function, and recount some of the principal tests for disturbance in this respect.

It is almost superfluous to offer here a reminder of the magnificent work of William Beaumont,¹ but so many of his conclusions remain uncontradicted to this day, and the inspiration which he gave to accurate methods of observation have so strongly influenced our present conceptions that some of his findings with respect to motility require repetition. For example, his deduction that

* Reprinted from the Archives of Internal Med., 1915, xvi, 406-428.

"the time required for the digestion of food is various, depending on the quantity and quality of the food, state of the stomach, etc.; but that the time ordinarily required for the disposal of a moderate meal of the fibrous parts of meat, with bread, etc., is from three to three and a half hours." Further, he drew the "inference," as he expressed it, "that oily food is difficult of digestion" and that "water, ardent spirits, and most other fluids are not affected by the gastric juice, but pass from the stomach as soon as they are received."

Cannon² also, by his painstaking experiments on animals, has given us reliable data, among which may be summarized the following: The chyme does not pass through the pylorus at the approach of every peristaltic wave, but emerges occasionally, at irregular intervals, of from ten to eighty seconds. Acid above opens and acid below closes the pylorus. Fats when given are almost invariably present in the stomach during seven hours' observation. Water begins to enter the intestine almost as soon as it enters the stomach. Carbohydrates go through rapidly; proteins more slowly. When carbohydrates and proteins are given one after another, the early rate of evacuation is largely the same as that of the first food given. Mixtures of carbohydrates and proteins have an emptying rate intermediate between that of carbohydrates and that of proteins. Fat retards the exit of either food-stuff from the stomach into the intestine. As to consistency of food materials, there is a marked retardation of the outgo of food from the stomach when hard particles are present. Considerable amounts of gas in the stomach retard the discharge of food. Rage, distress, anxiety, grief, anger, and violent emotions have a depressive effect on gastric motor activities.

Besides the physiologic variations to which the gastric clearance time is subject, it may also undergo numerous pathologic alterations, in the direction either of an exaggeration or a diminution of motility. Thus we are familiar with the shortened gastric evacuation time of non-obstructive duodenal ulcer and of non-obstructive cancer of the stomach. On the other hand, we are equally familiar with the retarded emptying resulting from so-called atony of the

stomach, hyperacidity, and reflex spasm of the pylorus, the latter either from an extrinsic cause, such as disease of the gall-bladder, or from an intrinsic cause, such as gastric ulcer. Further, and more importantly, we are acquainted with the gastric retentions produced by organic stenoses at or near the pylorus.

Now it would seem that by no simple test can sharp and constant lines of demarcation be drawn between hypermotility, normal motility, and hypomotility. Nevertheless, extreme variations in either direction, more especially toward hypomotility, have high diagnostic significance, can be determined at least broadly, and efforts at such determination cannot safely be neglected. The method in most common vogue, of testing gastric motility, is the administration of a meal and the use of the stomach-tube to ascertain whether food remnants are present after the lapse of a certain time. The following citations will give a fair idea of this method.

Kemp³ remarks that the impairment of the motor power is fully as important as, if not more important, in many cases, than, damage to the secretory functions. He describes various test-meals used in gastric analysis, including those of Riegel,* Ewald,† and Leube,‡ and the test-breakfast of Ewald-Boas.§ Regarding the specific question of motility he states:

“If, five hours after a test-meal, a small amount of chyme is aspirated, the motor power is good. If large quantities are found six hours after the meal, the motor function is absolutely (or, if stenosis, relatively) decreased. . . . Some employ the test-breakfast. Two hours later the stomach should be empty. If 100 c.c. or more are found at the end of an hour, or varying quantities at the end of two hours, it shows different degrees of motor insufficiency. The test-meal is more accurate. I sometimes administer a test-supper and aspirate in the morning to test the motor func-

* Riegel's test-dinner: Meat broth, about 400 c.c.; beefsteak, 150 to 200 gm.; mashed potatoes, 50 gm.; and a roll (35 gm.).

† Ewald's test-meal: Finely chopped meat, 175 gm.; stale bread, 35 gm.; and butter.

‡ Leube's test-meal: A plate of soup, a beefsteak, and a roll.

§ Ewald and Boas' test-breakfast: One or two rolls (35-70 gm.); one cup of tea or water (300-400 c.c.); given in the morning in the fasting condition.

tion, following immediately with the test-breakfast to examine the secretory function."

He also describes without comment the motility tests with salol (Ewald and Sievers⁴), iodopin (Heichelheim⁵), and oil (Klemperer⁶).

Bassler⁷ mentions as of value the Leube-Riegel test-dinner, consisting of beef-broth, 400 c.c.; beef, 150 gm.; pureé or mashed potatoes, 50 gm.; and a roll of wheat bread. The exit of this meal from the normal stomach should occur within five hours. But he goes on to say:

"A word of caution should here be given in assuming the existence of pathologic conditions when, five or six hours afterward, small quantities of food are extracted, for, while the great bulk of the meal is gone, tarrying remnants of food may be present in even the perfectly normal stomach up to the sixth and even the seventh hour after the time of ingestion. If at the sixth, seventh, or eighth, and so on, hour of extraction, after the taking of a mixed meal, considerable quantities of the meal constituents are obtained from a stomach, the existence of the following conditions should be considered, namely: Pyloric obstruction, states of atony, a more or less low state of digestive disturbance from degrees of subacute and chronic gastritis, accompanied with poor stomach function, and the existence of neurotic conditions of a depressing type affecting the entire motility of the organ. . . . Another form of examination by the extraction of stomach food contents to diagnose pyloric obstruction from any cause (particularly its high degree seen in malignancy) should be mentioned. In this the generally employed procedure is to advise the patient to eat a full meal in the early evening, and then to wash out his stomach the following morning—about ten or twelve hours afterward. Should the patient not have vomited during the night, and food remnants be found in the morning, bona fide pyloric stenoses can almost invariably be diagnosed."

He states further that a simplification of this method, which he can indorse as of much value, is the eating of several raisins* in the evening and noting if their skins or seeds are obtained in the morn-

* Bassler speaks of this as the "Mayo method." In fairness it should be said, however, that the addition of raisins to the Riegel meal is credited by Cohnheim (*Diseases of the Digestive Canal*, Edit. 2, Philadelphia, J. B. Lippincott & Co., 1911, p. 35) to Boas and Strauss.

ing lavage water. While in this test the obtaining of vegetable skins is of much significance, a negative result does not always mean that no stenosis exists. A less complete degree of stenosis, particularly in the pyloric region, but not directly at the pylorus, may give positive results with the six- seven- or eight-hour extraction of the mixed meal, but a negative finding with the raisin-skin method. The matter, he thinks, is entirely one of degree of stenosis; the nearer the stenosis to the pylorus, the more accurate are the results by both methods; the less the degree of the stenosis, or the farther away from the pylorus it is situated, the better is the result from the mixed meal, and the less so from the raisin-skin method.

Einhorn⁹ gives a fair summary of gastro-enterologic methods in common use when he says:

“The best and easiest way to test the motor function of the stomach is to examine this organ by means of the tube and lavage in the morning in the fasting condition after the ingestion of a substantial supper on the night previous. Normally the stomach is empty, and therefore when the organ is found to contain a quantity of food, this is the best sign of retarded motion.”

ROENTGENOLOGIC TESTS OF MOTILITY

Since the first employment of the roentgen ray in conjunction with an opaque meal for the diagnosis of gastro-intestinal disease, more or less attention has been directed to gastric motility. By a few men this feature of the examination is considered almost indispensable; by others it is regarded as of secondary importance, though usually given some attention, while a few deem it of little moment.

As might be expected, an investigation of the technic used by different roentgenologists shows considerable variance. Wide differences are noted as to:

1. The opaque salt used.
2. The character of the vehicle.
3. The proportion of opaque material to the medium of suspension.
4. The total quantity administered.

ROENTGENOLOGIC DETERMINATION OF GASTRIC MOTILITY 101

5. Management of the patient with regard to eating after the opaque meal has been taken.

Bismuth subnitrate, which was used in the first examinations of the digestive tract in man, produced toxic results in a few instances, and was superseded by bismuth subcarbonate or the carbonate, as it is called in Europe. A little later the oxychlorid of bismuth was used to some extent. On the continent a few have employed zirconium oxid. During recent years chemically pure barium sulphate has come into extensive use. So far as we are able to discover from the published observations of others and from our own experience, there seems to be little difference in the evacuation time of the various bismuth salts when given under equal conditions; but the difference in this respect between bismuth salts and barium sulphate is marked, the latter leaving the stomach distinctly earlier. Groedel's⁹ figures indicate that with barium sulphate, the stomach empties itself twice as fast as with bismuth.

The vehicles employed have been of every sort conceivable, including water, milk, mucilage of acacia, bread and milk, cereal porridges, paps and gruels, mashed potatoes, fermented milk, and mixed meals containing meat. The proportion of opaque salt to suspension medium varies from 10 to 50 per cent. of the former, and the total quantity of the meal given ranges from 6 to 20 ounces or more. Finally, practice differs as to permitting the patient to follow his accustomed habits of eating and drinking during the period of examination. Often this important feature is not mentioned, yet it is known that the taking of food after ingestion of the opaque meal will markedly prolong the evacuation time of the latter.

It is quite apparent that from these differing technics differing results must follow, and this undoubtedly accounts very largely for the varying esteem in which roentgen tests for motility are held.

The prototype of all the opaque meals now in use was that devised by Rieder,¹⁰ and consisted of 50 gm. of bismuth carbonate in 350 gm. of flour-pap. Rieder considered three to four hours as the normal emptying time for this meal. Commonly half the meal is discharged within an hour. He remarks that toward the end of digestion there is a distinct slowing of emptying, which he thinks

is due to an intestinal reflex. He mentions the experiments of Wulach showing the emptying time of carbohydrate mixtures to be from two and one-half to three and one-half hours, albuminous mixtures five or six hours, and fat from seven to eight and one-half hours. The roentgen method gives a good picture of gastric motility. But, Rieder adds, in spite of the great excellence of the roentgen motility test, the method formerly used alone, of withdrawing a test-breakfast or test-meal, will firmly retain its diagnostic worth, because it will show in every case not only the motility, but also the secretory function.

Barclay¹¹ has used bismuth carbonate in the proportion of 1 to 2 or 3 of the excipient, for which latter he employs bread and milk, thoroughly mashed up, or porridge. The total quantity given varied from 2 to 12 ounces. With regard to motility he says:

"Retention of bismuth food is the result of pyloric obstruction, and Rieder laid it down that the whole of a bismuth meal should have left the stomach within five hours. For diagnostic purposes this is a good enough guide, but I never report definite obstruction unless the delay is well marked. In hospital practice eight hours' retention is my standard, but in the vast majority of the cases recorded some food was still present in the stomach after twenty-four hours. In private practice six hours is my standard, but I always repeat the observation on at least one occasion to verify this finding when the margin of delay is so small."

Groedel¹² at first employed the Rieder carbohydrate meal. An emptying time beyond four hours he regarded as abnormal. Later he¹³ began using barium sulphate, 250 gm., mixed with 20 gm. each of maize flour, sugar, and cocoa in 400 c.c. of water. This meal, he found, emptied normally in two hours.

Kaestle¹⁴ considers two and one-half to three and one-half hours as the normal emptying time of a fluid, carbohydrate (mondamin), contrast meal containing zirconium oxid and weighing 400 gm. A stiff mixture of the same weight may require four hours. Slight delay of evacuation of the fluid meal, up to six hours, he states, may be caused by gastric atony, hyperacidity, reflex pylorospasm, and even beginning pyloric stenosis. Residues after twelve hours or

longer occur only with organic pyloric stenosis. Hypermotility may result from a gaping pylorus or strong expulsive energy (hyper-tonus and hyperperistalsis).

Satterlee and LeWald,¹⁵ in their description of the water-trap stomach, remarked the occurrence of a residue from the bismuth meal in many of these cases. "The water-trap stomach," they say, "might almost be considered as a ptosed organ, with the first portion of the duodenum and the pylorus fixed in proper position, giving the characteristic long pyloric arm and resemblance to a water-trap." The meal given consisted of 90 gm. of bismuth subcarbonate, suspended in 600 c.c. of fermented milk. A residue from this meal, "long after the usual emptying time," was noted in 50 per cent. of the cases. In their conclusions they state: "The typical water-trap stomach of marked degree, which shows a large residue in the stomach after six hours, should be operated on when diagnosed."

Cole¹⁶ remarks:

"I have already shown the fallacy of testing the gastric motor efficiency by administering bismuth suspended in fluid or mixed with cereal, and the same is true for intestinal motor efficiency. If the test is to be of value, the stomach and intestines must be called on to evacuate such a meal as is normally imposed on them. Therefore, the true test of gastro-intestinal motor efficiency is made by administering bismuth or barium suspended in fluid, preferably buttermilk, in conjunction with a Riegel meal of meat, potatoes, and bread. . . . If the stomach is high and of the cow-horn type, especially if a condition of diminished acidity or achylia exists, evacuation will be accomplished very rapidly, perhaps in two hours, whereas many a stomach presenting no organic obstruction requires six hours for complete evacuation."

Baetjer and Friedenwald¹⁷ gave a meal consisting of bismuth subcarbonate, 1½ ounces, in an ordinary glass of water (about 12 ounces), with sufficient mucilage of acacia to make an emulsion. In obstruction from within (pyloric carcinoma, ulcer with cicatrix, idiopathic thickening of the pylorus) they noted gastric retention for from ten to twenty hours. In obstruction from adhesions from

chronic appendicitis or after appendectomy retention for from six to eight hours was found. Gall-bladder adhesions showed residue in the stomach after five or six hours. Retention from muscular relaxation (atony) was also observed, but the time factor is not given. They regard from three to four hours as the normal emptying time for a horizontal stomach; from five to six hours for a prolapsed fish-hook stomach.

George and Gerber¹⁷ call attention to the fact that the original Rieder meal contained 50 gm. of bismuth subcarbonate in about 400 c.c. of cooked cereal. Later other mediums and much larger amounts of the opaque salts came into use.

"As a result of the marked variation of bismuth meals it is impossible to use the same functional data for diagnosis. . . . This is a point which has not been appreciated by many roentgenologists. They have used various kinds of meals—not only buttermilk, but malted milk, plain milk, water, mashed potato, etc., and have varied the amount of bismuth or barium, and yet have attempted to apply to their work the conclusions based on the observation of functional disturbances in thousands of cases done under the Rieder technic. Obviously this is incorrect. The only proper course left for one who wishes to use these functional data is to accumulate a large number of cases, done with more satisfactory mixtures, and check them up with operative results."

In a paper written a few months prior to the above George and Gerber¹⁷ venture this statement: "The more we have accumulated evidence on this subject, the more we have become convinced that six-hour gastric stasis is the least important factor in roentgen bismuth diagnosis." Recently they²⁷ have reiterated this opinion. It should be noted that with their technic the patient is permitted to take food during the six-hour period.

White and George²¹ observe that ulcer in some other part of the stomach may cause such spasm of the pylorus that bismuth is retained for a long period, even up to twenty-four hours, while operation shows the pyloric walls perfectly normal. A considerable residue in the stomach at the end of six hours, with no anatomic defect and nothing found elsewhere to explain it, suggests

gastric ulcer, but it is to be remembered that the stomach empties itself entirely in six hours in about one-half the cases of gastric ulcer. These authors state further that the emptying of the stomach depends on several more or less opposing factors, namely, gastric peristalsis, mechanical obstruction at the pylorus or in the duodenum, and the reflex control of the opening and shutting of the pylorus. Ulcer of the duodenum may disturb this reflex, and when acid chyme is squirted into the duodenum, the absence of the reflex allows the pylorus to remain open or relaxed, and thus permits rapid emptying of the stomach. They go on to say that when indurated duodenal ulcer or scar tissue or adhesions cause mechanical obstruction, the result depends on the balance of the opposing forces; the stomach emptying in the normal time or earlier or later, according as the obstruction overcomes the tendency to rapid emptying which results from active peristalsis or interference with the pyloric reflex.

As a test of motility in those cases in which the stomach-tube is contraindicated or refused, Bassler²² uses a mixed-meal method by which he gives 25 gm. of bismuth subcarbonate with the Riegel meal and examines by the roentgen ray six hours later, at which time the stomach should be empty. In marked pyloric stenosis he has noted a residue at twelve hours, or much later—even to five days. However, in a subsequent publication, Bassler²³ has this to say:

“In the study of motility and exit from the stomach in 203 cases of distinct gastroparesis, in which hourly roentgen-ray observations were made, the conclusion was plain that the roentgen-ray method of diagnosing stasis in the stomach is not as practical as the test-meal method. One hundred and twenty-six of these cases examined by the bismuth-roentgen-ray method showed delay of exit of six hours or more, while only 31 showed the delay by the test-meal method. . . . Instances were encountered in which bismuth was present in the stomach as late as eighteen hours after ingestion, while the stomach on a mixed meal was empty in four and one-half hours. . . . It is apparent, whatever has been advanced to the contrary, that the method of examination by food extraction is decidedly more to be depended on in gaining an idea of exit from the

stomach than is the bismuth-roentgen-ray method, for it was strongly suggested that foods pass from the stomach in decidedly less time than will bismuth or any other form of metal salts used to throw a shadow, probably because of the pulverized salts adhering to the mucosa.

The most faithful advocate of the roentgen motility test is Haudek,²⁴ and to him we are indebted for the double-meal method of examination, the establishment of the six-hour limit, and a vast deal of information concerning the significance of disordered motility as shown by the roentgen ray. The rather chaotic application of the roentgen examination for motility led Haudek, in 1909, to establish his double-meal method, partly with the view of saving time and partly to make the test more precise. Accordingly he began the administration of a Rieder meal in the morning, and examined the patient six hours later, at which time a second Rieder meal was given to complete the examination. The selection by Haudek of six hours as the division line between normal and delayed emptying was explained by him on the ground that while the normal stomach will drive out a Rieder meal in about three hours, as an average, delay to five or six hours might result from physiologic causes. He cited as examples the influence of rest and movement, right and left-side positions, psychic factors, eating or drinking after taking the meal, and sedimentation of the opaque salt. Even after six hours or longer minute residues might sometimes be found in normal stomachs, and he accordingly ignored mere traces. Small residues, up to a quarter of the meal, he deemed, could be due not only to organic pathologic changes, but also to hypomotility from atony, hyperacidity, or long *hubhöhe*, that is, a long, vertical pars pylorica. Larger residues could be almost certainly ascribed to pyloric obstruction by organic stenosis or spasm from ulcer. He also pointed out that the test did not rest alone on the presence or absence of a residue, but that the position of the "head" of the six-hour meal gave gross information as to motility. Normally at or near the cecum the "head" would be advanced far into the large intestine by hypermotility, or held back in the small intestine by hypomotility. Further, on giving the second meal, there could also

be taken into consideration the tonus of the stomach, its peristalsis, the freedom of passage through the pylorus, the *hubhöhe*, and thus the total picture would enable an estimation of "the great X of motility, the functioning of the pylorus."

An experience of years with thousands of cases has increased Haudek's confidence in the method. In a recent article he²⁵ goes so far as to say that the roentgen determination of the expelling forces of the stomach gives better results than the older methods, and that it is not only exact and reliable, but also very simple. He shows that while the clinical examination cannot determine whether the increase or decrease of motility is due to a change of the expelling power or of the resistance, the roentgen examination can be much more decisive. While he had previously considered atony to be an occasional cause of six-hour retention, he now believes that atony, under otherwise normal conditions, causes only a slight increase of evacuation time—usually below six hours. The most important factor for the evacuation of the stomach is the condition of the pylorus. Lessening of resistance produces the picture of pyloric insufficiency; an increase leads to the highest degrees of stagnation. He enumerates the common causes of increased resistance, both organic and spastic, and cites examples as varied by the functional components of motility. He also mentions Sahli's method of testing the motility with sinking and swimming capsules in differentiating between pylorospasm and organic stenosis, also the effect of papaverin in these conditions. By means of Sahli's capsules the evacuation time of water can be shown; this is usually normal in pylorospasm, but prolonged in stenosis. According to Holzknecht, the administration of papaverin shortens the emptying time in pylorospasm to normal, increases it in stenosis, and has no effect on a combination of the two.

For more than two years past our work has been based on the double meal method of Haudek, and we can unreservedly indorse his claims. For various reasons we have found it advisable to modify his technic in some particulars, but have retained the six-hour limit and adhered rather closely to his general principles. A cereal porridge instead of a pap for the six-hour meal is employed,

and barium sulphate* substituted for bismuth salts. Since barium leaves the stomach earlier than bismuth we believe that a six-hour retention of barium is even more significant than one of bismuth. Until the first of this year patients were required to take castor oil on the evening previous to the day of examination, but this has been abandoned as unnecessary. The observations of Hayes²⁶ show that purgation results in a heightening of gastro-intestinal motility for a day or two. A comparison of our observations during the past few months with those made previously indicates that this increase does occur, but that it does not materially affect the six-hour test. Our present routine is as follows:

The patient comes to the laboratory in the morning without breakfast, and usually, but not always, after tubing and lavage by the gastro-enterologist. He is given a meal consisting of four ounces of well-cooked wheaten breakfast cereal with two ounces of barium sulphate, to which he is permitted to add a little milk and sugar according to his taste. He is instructed to take neither food nor drink, except water, until the examination is finished. Six hours later he returns and the screen examination is begun. The presence or absence of a residue in the stomach from the motor meal is noted. The amount of retention is recorded on a scale of four units, each unit representing approximately a fourth of the meal. If the entire meal has passed into the intestine, its position and distribution are observed. The patient is then given two ounces of barium sulphate stirred up with eight ounces of water. Usually some of this escapes or can be driven through the pylorus, showing its condition as to patency. To complete the examination and to fill the stomach for roentgenography, the patient takes about twelve ounces of a potato-starch pap containing approximately three ounces of barium sulphate, after which the behavior of the stomach in all respects is watched.

Our gastro-enterologist's routine for examination of the gastric contents is the following:

At 6 P. M. previous to the day of examination the patient takes

* As is well known by roentgenologists, only chemically pure barium sulphate is used, other salts of barium being absorbable and toxic.

a modified Riegel meal, that is to say, he is instructed to eat an ordinary meal which must include bread, meat, and potatoes. An hour later he eats 20 raisins, the skins of which are easy of identification, and tend to remain in the stomach somewhat longer than the usual food materials. The gastro-enterologist's examinations are begun the next day, about 8 A. M., and, depending on the number of patients to be examined, the interval after the motor meal varies from fourteen to sixteen hours. The estimate of motility is based on the presence or absence of food-bits or raisin-skins from this meal, as shown by tubing at the morning examination. Residues are recorded on a scale of 4. The gastro-enterologist's technic also includes the administration of a modified Ewald test-breakfast for the chemical examination, but with this we are not here concerned.

COMPARISON OF THE RESULTS IN 950 CASES

During the year 1914, 950 patients who had been examined both by the roentgen ray and the test-meal went to operation. Two hundred and twenty of these, or 23.1 per cent., showed a gastric residue, at the roentgen examination, from the six-hour meal. One hundred and thirty-one, or 13.7 per cent., had food remnants. In other words, the roentgen ray showed approximately 70 per cent. more retentions than did the clinical test-meal. The lesions found were: Disease of the appendix, 125 cases; disease of the gall-bladder, 311; gastric ulcer, 109; gastric cancer, 137; duodenal ulcer, 268. The accompanying table shows the incidence of retention in each of these conditions, as shown by the roentgen ray and stomach-tube respectively. The preponderance of six-hour barium residues over food remnants from the test-meal is noteworthy, being twice as great in gastric ulcer and lesions of the gall-bladder; almost twice as great in duodenal ulcer; and half again as large in gastric cancer. In the 125 cases with lesions of the appendix a retention was noted by the roentgen ray in only one case, and found in two cases only by the stomach-tube. In only 12 of 311 cases with lesions of the gall-bladder was retention noted either by the Roentgen ray or by tubing. The vast majority, 209 (90.4

per cent.) of the 220 patients showing a barium retention were found at operation to have cancer or ulcer of the stomach or ulcer of the duodenum.

In 16 cases representing all five conditions the stomach-tube revealed food remnants, while no six-hour retention of barium was found by the roentgen ray. On the other hand, 105 patients had roentgen residues, but no food remnants.

In 8 of the cases tabulated under gastric ulcer there was also duodenal ulcer. All these patients showed a residue from the barium meal, and 6 of them had food remnants.

INCIDENCE OF RETENTION OF TEST-MEAL IN 950 CASES

	TOTAL NUMBER	WITH RESIDUE (X-RAY)		WITH FOOD REMNANTS (TUBE)		WITH RESIDUE (X-RAY) ONLY		WITH FOOD REMNANTS (TUBE) ONLY		WITH BOTH RESIDUE (X-RAY) AND FOOD REMNANTS (TUBE)		NUMBER WITHOUT RESIDUE (X-RAY) OR FOOD REMNANTS (TUBE)	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.		
Lesions of the appendix	125	1	0.8	2	1.6	1	0.8	2	1.6	0	0.0	122	3
Lesions of the gall-bladder	311	10	3.2	5	1.6	7	2.2	2	0.6	3	0.9	299	12
Gastric ulcer	109	50	45.8	25	22.9	29	26.6	4	3.5	21	19.2	55	54
Gastric cancer	137	83	60.5	57	41.6	29	21.1	3	2.1	54	39.4	51	86
Duodenal ulcer	268	76	28.3	42	15.6	39	14.5	5	1.8	37	13.8	187	81
	950	220	23.1	131	13.7	105	11.0	16	1.6	115	12.1	714	236

Besides the cases tabulated above, residues were found by the roentgen ray in one patient in each of the following conditions: Cancer of the pancreas, tumor of the ileum, cancer of the common duct, hydronephrosis, tumor about the head of the pancreas, tumor of left kidney, subdiaphragmatic abscess, and cancer of the ascending colon. In the four first mentioned, retention was also noted by the gastro-enterologist.

How can the discrepancy between the gastro-enterologist's results and our own be explained?

First, it would seem probable that the time elapsing between the ingestion of the gastro-enterologist's meal and its withdrawal

is too liberal, and that the stomach was empty in many cases, although an actual and pathologic hypomotility existed.

Second, it is quite possible that the tube may have failed occasionally to bring up food remnants which were present. Harmer and Dodd,²⁷ by watching with the roentgen ray the introduction of the tube, frequently noted that the tip impinged against the gastric wall, well above its most dependent portion, and continued efforts to pass the tube simply caused it to curl and displace the tip further upward. In other instances it was found that by passing the usual length of tube in cases of ptosis, the tip might fail to reach the residuum. This, they believe, is a common error. The posture of the patient and the position the stomach occupies in the abdominal cavity affect the success of tubage. From their observations they regard it as "obvious that failure to recover gastric residuum with the unaided stomach-tube from a fasting stomach or after the ingestion of a test-meal cannot be accepted as conclusive evidence of the absence of gastric stasis." Rehfuss, Bergeim and Hawk²⁸ have employed a tube devised on the principle of the duodenal tube, with a slotted metal tip, which, by its weight, will seek the most dependent part of the stomach. In instances in which the passage of the ordinary tube failed to disclose any residue the new tube obtained considerable amounts. They found, further, in a series of healthy persons, that the fluid residuum in the normal empty stomach far exceeded the accepted limit of 20 c.c., and in several was above 100 c.c.

Third, the tube may have failed to reach food retained in the lower locus of an hour-glass stomach. It seems probable that this occurred in at least one instance of hour-glass stomach where the roentgen ray showed a residue, but the gastro-enterologist reported none.

Fourth, marked differences as to the quantity and character of the food taken by the patient may have affected the gastro-enterologist's results.

Fifth, in exceptional instances of organic stenosis at the pylorus (cancer or ulcer) the tube found retained raisin-skins when the roentgenologic test failed to show a barium retention. It is

clear that a stenosis might be sufficiently narrow to block the passage of these skins, yet permit a fair exit of finely divided barium.

APPLICATION OF THE ROENTGEN TEST

It is evident that the double-meal method does not, as a routine, concern itself with hypermotility in terms of exact time of evacuation, although this can be established with either the first or the second meal if desired. As a rule, the degree of hypermotility can be reckoned by the advance of the head of the first meal beyond the cecum, plus the freedom and continuity of exit of the second meal through the pylorus. It is true that the position of the six-hour meal is the net result of the motility both of the stomach and intestine, but in the absence of intestinal obstruction as shown by other roentgen signs, or severe obstipation or diarrhea, as indicated by the anamnesis, the intestinal factor can be disregarded.

In the presence of an evident hypermotility we have to consider as possible causes duodenal ulcer, gastric carcinoma, anacidity, and diarrhea. The report of the gastric analysis or the clinical history will decide as to anacidity or diarrhea, respectively. The most typical hypermotility is seen in cancer, with its gaping pylorus, which may be infiltrated and stiffened or merely relaxed by the anacidity. The flow through the pyloric opening is continuous and frequently voluminous, and the six-hour meal may have advanced into the transverse colon or beyond. The hypermotility of gastric cancer is not incompatible with actual narrowing of the pylorus, which remains steadily open and thus more than compensates for the narrowing. Over 90 per cent. of the gastric cancers will reveal direct roentgen evidence (filling defects), so that hypermotility is by no means a principal sign. The hypermotility of duodenal ulcer is commonly attributed to interference with the pylorus-closing reflex, as well as to hypertonus, and hyperperistalsis. Here, again, these factors may balance or even overcompensate a slight organic or spasmodic stenosis at the site of the ulcer. In any event, most of the cases of duodenal ulcer will show hyperperistalsis or other diagnostic signs in the way of an accessory pocket or deformity of the bulb.

An initial rapid rate of clearance of the second barium meal through the pylorus is not alone a dependable sign of hypermotility; the advancement of the six-hour meal in the colon should also be considered. We have seen numerous cases of cholecystitis (with and without periduodenal adhesions), chronic appendicitis, hypochlorhydria from all causes, and general reflex gastrospasm, in which the clearance was large and uninterrupted during five or ten minutes' examination, yet this clearance was probably not characteristic of the whole period of digestion, since the six-hour meal was not advanced beyond its average position.

By the process of elimination few cases of actual hypermotility remain unexplained, and, on the whole, it is of less practical importance than its converse.

With the stomach empty at the end of six hours and the head of the motor meal anywhere from the cecum to the hepatic flexure, the gastric motility is considered normal, at least so far as the net result is concerned. It does not follow that this finding absolutely excludes any disturbance of either the active or passive factors of motility, since a diminution of one may be offset by an exaggeration of the other. For example, a somewhat stenotic pylorus or duodenum may be balanced by vigorous gastric peristalsis or an achylia; or a so-called atonic stomach with weak peristalsis may evacuate its contents through an unusually patent pylorus in average time. Hence a stomach that is empty at six hours, with the motor meal at or not far beyond the cecum, is, strictly speaking, normal as to motility only on condition that other elements are normal also, that is, acidity, peristalsis, tonus, and pyloric functioning. If any of the latter are definitely abnormal, the presumption is that one abnormality is compensated by some other, and an analysis of the complication may promote diagnostic nicety. With our present limitations, however, a calculation of this sort could easily lead to error by its intricacy. Likewise, between the average emptying time of say three hours and the arbitrary limit of six hours allowed for presumptively normal evacuation, is a rather wide zone for the play of physiologic and occasionally pathologic, factors causing hypomotility. It was precisely to make liberal

allowance for these that Haudek drew his line at six hours, and for this reason we have adhered to that line, though our meal probably leaves the stomach earlier than Haudek's. If there is error it is, at all events, on the side of safety. For emptying times greater than three hours but less than six hours, there is a host of possible causes, including depressive psychic states, weak peristalsis, hypotonus or so-called atony, high *hubhöhe*, ptosis, hyperacidity, reflex spasm of the pylorus, and slighter grades of stenosis, whether uncompensated or only partially compensated. In many cases, although the stomach is empty at six hours, retarded evacuation is evinced by the motor meal lying proximal to the cecum, together, sometimes, with scanty initial clearance of the second meal. Often the cause of this moderate hypomotility is manifest in the form, position, peristalsis, or tone of the stomach, or the functioning of the pylorus. In our own experience organic stenoses causing delayed gastric evacuation, but within six hours, have been relatively rare. Shortening the time limit to say five hours in order to detect such cases would probably result in greater error by including physiologic and functional delays.

The six-hour limit allows for delay resulting mainly from weakened active factors of motility—tonus and peristalsis. Delay beyond six hours signifies, as a rule, some disturbance of the passive factor, namely, organic or spastic obstruction at or near the pylorus. It should be reiterated that this delay must be shown by a substantial and visible residue, not mere traces held in the gastric folds, nor a collection in the lower pole so small that it can be seen only with difficulty. With a retention of one-fourth or more of the meal, either obstruction of an organic character probably exists or a serious lesion interfering reflexly with emptying. Among the causes of organic obstruction we have noted duodenal and pyloric ulcer with cicatricial contraction, hypertrophic pyloric stenosis, pedunculated benign tumors (polyposis), pyloric carcinoma, syphilis of the stomach, carcinoma of the upper jejunum, and adhesion bands from inflammatory processes in the right upper abdominal quadrant, usually pericholecystitis. Other causes of obstruction mentioned in the literature are foreign bodies (hair-balls, fruit-stones,

etc.), kinking of the prolapsed stomach at its duodenal anchorage, adhesions from chronic appendicitis, and tumors outside the duodenum pressing on it, although we have not encountered a six-hour retention attributable to any of these, except possibly the last.

Small residues down to an eighth or less of the motor meal may, of course, also result from organic narrowing. A commoner cause is spasm of the pylorus occurring reflexly from a lesion of the stomach itself, such as ulcer, or from an extrinsic pathologic focus, most often the gall-bladder or appendix, and also, but rarely, from more remote abdominal lesions. Holzknecht²⁹ has remarked the possibility of a six-hour bismuth residue from pyloric spasm due to morphinism, or a single administration of morphin at the time of examination.

In explaining the mechanism by which gastric retentions are produced in the absence of an organic stenosis, roentgenologists have frequently assigned "pylorospasm" as a cause. Now, by the clinician, the term is limited to a spasmodic contraction of the pylorus accompanied by pain, vomiting, etc., occurring commonly as a symptom of extragastric conditions, for example, disease of the gall-bladder. Roentgenologically, the word has been used rather broadly, perhaps somewhat loosely, to cover an irritable, or hyper-tonic, or spastic pylorus, which relaxes less freely or less frequently than the normal pylorus, regardless of symptoms.

As a matter of fact, a pylorus which is not organically stenosed is not infrequently seen to remain closed continuously or for abnormally long periods during the roentgen examination of anatomically normal stomachs showing a six-hour retention, and whether or not the term "pylorospasm" be strictly applicable, the condition cannot be ignored as a probable cause of gastric retention.

As remarked previously, Haudek has mentioned the high *hubhöhe*, that is, a long, steeply ascending pyloric arm, as a cause of hypomotility. Of very similar character is the "water-trap stomach" of Satterlee and LeWald, in many cases of which, with their technic, six-hour residues were noted. In both these conditions there is usually a degree of gastric atony. Cannon³¹ holds that, in the normal stomach, drainage by gravity is an unfortunate

conception, that the food is in exact equilibrium, and that muscular action is necessary to its progression. Haudek claims, on the other hand, that the existence of an impeding action of a high level of the outlet has been shown experimentally, as there is a shortened evacuation time in the right lateral position and a prolonged evacuation time in the left lateral position. Neilson and Lipsitz³² have found, from experiments on healthy young men, that lying on the right side produces a more rapid evacuation of water than does any other position, and that lying on the back causes a quicker emptying than the upright posture. In the light of these statements it would appear that while gravity probably plays a minor rôle in gastric evacuation, as compared with other factors, it cannot be altogether disregarded. Whether a high situation of the pyloric outlet, without an associated gastric atony, may or may not cause a delay of evacuation, we have not noted such delay go beyond six hours with the barium meal. Nor have we noted a six-hour residue attributable simply to hyperacidity, atony, or intestinal stasis with or without "kinking of the duodenum." While the motility of the stomach in a given case is susceptible of some variation from time to time, we have seldom seen a six-hour retention which did not recur at a subsequent examination. But, in the case of a residue without any other diagnostic indications, the test with the motor meal should be repeated before drawing conclusions. On the whole it would seem that Holzknacht was not speaking extravagantly when he said: "Haudek's method of the double bismuth meal has at one step promoted the motility test to the first place in the roentgen examination of the stomach."

The interpretation of the results from the double-meal method may be either simple or complex, as desired. The observer may be content with determining the presence or absence of a residue at the end of six hours. With the presence of such a residue he can be fairly certain of organic pathology somewhere in the gastro-intestinal tract, and probably in the stomach or duodenum. Again, he may also take cognizance of hypermotility or lesser degrees of hypomotility. Still again he may consider the results in the light of all the discoverable factors pertaining to motility, including the gas-

tric form, position, tonus, peristalsis, and acidity. Finally, he may combine and correlate his findings with other roentgenologic signs, the physical examination, and the clinical history. By the construction of "symptom-complexes" in this manner Holzkecht³³ was enabled to make diagnoses which otherwise could not be made, and we have routinely followed this plan to advantage. While this has been criticized as an "indirect" method in comparison with the "direct" method, namely, that of proving the presence of a lesion by showing local deformity of contour, we can only say that we have often failed to discover such deformity although the symptom, and sign-complex established the diagnosis. Certainly deformity of contour is of the highest roentgenologic value and should be zealously sought for, but, like all other signs, it fades gradually into the realm of uncertainty. A six-hour residue is a strong stimulus to careful search for direct signs, and, if the latter are found, the presence of a retention is added assurance that the eye is not deceived, that a lesion exists, and that it is interfering with motility, which latter information is important to the surgeon. A diagnosis which takes into account all the facts obtainable from all sources is less likely to go astray than one which rests on a single phenomenon.

Gastric retention can be combined into various indicative complexes. A six-hour residue with a stomach of normal contour, showing hyperperistalsis, means obstructive duodenal ulcer more than ninety times out of a hundred. Residue plus an apparently normal gastric outline, plus an irregular, vigorous peristalsis, chiefly on the greater curvature, usually signifies a lesion involving the pylorus. A residue with an achylia, but without gross alteration of the gastric contour, should suggest the probability either of a small obstructing pyloric carcinoma, or obstruction of the duodenum by pericholecystic adhesions; careful attention to the pyloric and duodenal contours will usually make the distinction. Residue with hyperacidity and no irregularity of the gastric or duodenal outline would indicate a stomach reflexly affected by some other abdominal condition, notably cholecystitis or appendicitis. Innumerable but practicable complexes can be formulated by the introduction of

other related data. We have on other occasions emphasized the importance of a general correlation in every case.

The possibilities of the roentgenologic estimation of motility are by no means exhausted. The method described in detail deals with the evacuation of a carbohydrate meal only. We can freely endorse its convenience and trustworthiness in the diagnosis of the graver and usually surgical conditions. By a mixed meal and an extension of the time limit, or by examination at short intervals, or by testing the motility of each individual for carbohydrates, proteins, and fats separately, the diagnosis of slighter disturbances of motility, amenable to medical treatment, might be assisted. But, with all the work of the experimental physiologists before us, no meal can be devised the normal emptying time of which can be foretold with certainty, and any test must be proved by trial with an abundant material.

As a caricature may sometimes serve to show the truth better than a photograph, so a diagrammatic representation of motility may assist a clearer understanding. Taking as a basis a meal which leaves the normal stomach in an average time of say three hours, such as the bariumized carbohydrate meal, we may divide gastric evacuation time as represented on a scale of hours into three zones, viz.:

1. A zone of normal motility.
2. A zone of pathologic hypermotility.
3. A zone of pathologic hypomotility.

1. The zone of normal motility must extend from an emptying time somewhat less than three hours to an emptying time somewhat greater than three hours, since we can fix the three-hour point only as an average, on either side of which a variation may be due to purely physiologic causes. Within this zone we are also obliged, as a conservative measure, to include slighter tendencies to hypermotility or hypomotility from causes which, though pathologic, are not pronounced or are compensated wholly or in part. General knowledge justifies the assumption that such variation toward hypermotility is not wide, and, for the purpose of this diagram, we may choose the two-hour point as the normal minimum. The

variation toward hypomotility we may grant to be much wider; Haudek makes a generous allowance to the end of the sixth hour, which we will accept. The contents of this normal zone would then include:

(a) Normal motility. (Example: A normal stomach functioning in a normal manner.)

(b) Early emptying, physiologic. (Example: A hypertonic, steer-horn stomach.)

(c) Early emptying, pathologic, but partially compensated. (Example: Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of an associated hyperperistalsis, hypertonus, and free pyloric patency.)

(d) Disordered motility with abnormal but balanced factors. (Example: Stenosing carcinoma with achylia, yet with a net emptying time of three hours.)

(e) Delayed emptying, physiologic. (Example: A somewhat hypotonic fish-hook stomach.)

(f) Delayed emptying, pathologic, but partially compensated. (Example: Stenosis with hyperperistalsis, emptying being retarded, but within six hours.)

2. The zone of hypermotility, restricted to an emptying time less than two hours, would include such frankly pathologic conditions as non-obstructing gastric carcinoma, duodenal ulcer, and diarrheic conditions.

3. The zone of hypomotility, beyond six hours, would comprise the stenoses, both organic and spasmodic, as examples of which may be mentioned obstructing pyloric carcinoma or ulcer, markedly obstructing duodenal ulcer, and reflex pylorospasm from disease of the gall-bladder, or gastric ulcer remote from the pylorus.

As a matter of fact, we know that these zones may overlap each other and that time alone will not delimit normal from abnormal motility. The diagram, while somewhat practical in a way, illustrates the time factor only, and, as said before, a final opinion must rest on an analysis of all the factors. By the roentgen method this analysis is both possible and practicable, and herein lies its superiority to the test-meal and tube.

	Hour
Zone of Hypermotility . .	0
	1 Early emptying, pathologic. (Non-obstructing gastric carcinoma. Duodenal ulcer. Diarrheic conditions.)
	2
Zone of Normal Motility	Early emptying, physiologic. (Hypertonic, steer-horn stomach.)
	3 Early emptying, pathologic, but slight, or partially compensated. (Duodenal irritation. Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of associated hyperperistalsis, hypertonus, and free pyloric patency.)
	4 Normal emptying. (A normal stomach functioning in a normal manner.)
	Disordered motility with abnormal but balanced factors. (Stenosing carcinoma with achylia; average emptying time.)
	5 Delayed emptying, physiologic. (Hypotonic fish-hook stomach.)
Zone of Hypomotility . .	Delayed emptying, pathologic, but slight or partially compensated. (Slight stenosis. Stenosis with hyperperistalsis; evacuation retarded but within six hours.)
	6
	Delayed emptying, pathologic.
	Stenosis:
	7 (a) Organic. (Obstructing pyloric carcinoma. Pyloric ulcer. Obstructing duodenal ulcer. Periduodenal adhesions, etc.)
	(b) Spasmodic. (Reflex pylorospasm from ulcer on the lesser curvature, cholecystitis, appendicitis, and remote abdominal lesions.)
	8
	etc.

CONCLUSIONS

1. It would seem that the bariumized carbohydrate meal described above is a more sensitive test for gastric motility than the modified Riegel meal as commonly used in the Mayo Clinic.

2. The roentgenologic double-meal method is more informative than tubing after a motor test-meal, since the former not only shows delay of evacuation beyond six hours, but also yields information as to hypermotile conditions, and often, by showing both the active and passive factors concerned in motility, aids in the judgment of the net result.

3. A distinct residue after six hours from the barium meal given under the conditions prescribed has been, nine times out of ten, in

our experience, indicative of grave pathology and usually denotes obstruction at or near the pylorus.

4. The roentgenologic method is probably capable of further elaboration and refinement. By this means the motility of the stomach for various food-stuffs, given separately and in combination, can be determined with ease and accuracy, and by such determinations the diagnosis of gastric disorders might be further promoted.

5. The six-hour barium residue may be the most definite and striking roentgenologic sign of a gastro-intestinal lesion. Other signs may be so slight and indefinite that a diagnosis might not be ventured without this retention.

6. Retention of the barium meal is often an important element in roentgenologic syndromes as used in diagnosis. In the absence of other decisive Roentgen manifestations this finding may have considerable value in correlation with the clinical data.

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ROENTGEN DIAGNOSIS OF GASTRIC CANCER, WITH SOME ILLUSTRATIVE CASES *

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In the detection of cancer of the stomach, the roentgen rays take precedence over all other methods, despite the fact that "we are only in the daguerreotype stage of roentgen-ray photography."¹ In the Mayo Clinic, 95 per cent. of gastric carcinomas are discovered by this means, a percentage which is not approached by any other process of examination.

Since nearly one-third of all cancers occur in the stomach, and since early recognition and operation alone afford a chance of cure, any measure which will increase the number of correct and early diagnoses is of the highest importance.

Prior to the development of gastric roentgenology, diagnostic reliance had to be placed upon the history, the physical examination, and the gastric analysis. Significant in the history were: middle or advanced age of the patient; digestive disturbance, such as anorexia, vomiting, occasionally pain, hematemesis, etc.; cachexia and loss of weight. By the physical examination the presence of a tumor was sought. The gastric analysis was scanned for achlorhydria, food remnants, blood, and Oppler-Boas bacilli.

It is quite clear that the most important of these evidences can result only from a cancer which is well advanced or one which is obstructive. The records of our clinic show that in a large series of cases confirmed by operation, 67 per cent. of the patients had palpable tumors and 53.3 per cent. had food remnants. In other words, 33 per cent. had no palpable tumors and 46.7 per cent. had no food remnants to indicate obstruction. It is precisely in those

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cases which show neither tumor nor food remnants that the roentgen rays have their greatest field of usefulness and superiority. It is no longer necessary to wait until the tumor is palpable or until evidences of marked obstruction exist.

There is no intent to say that the clinical data should be discarded. On the contrary, the roentgenologist should in every instance be acquainted with the clinical facts. If suggestive of cancer, they will stimulate him to a more exhaustive search. If negative, they will exercise a wholesome restraint upon his interpretation of the reflex phenomena so often produced by conditions outside the stomach. More important still, the final diagnosis should be compatible with all the findings, if possible, and occasionally only their correlation will make the diagnosis. A combination of all methods forms a net through which few cancers will escape.

It must be conceded that the carcinomatous character of tissue can be positively determined only by the microscope, and the roentgen rays can merely show the presence of a gastric tumor, which may or may not be malignant. However, benign gastric neoplasms are uncommon; according to Graham,² 95 per cent. of tumors of the stomach are cancer. Further, in the occasional instance of a non-malignant new growth, if the salient features of the clinical history are considered, the diagnostician will be at least suspicious of the fact.

The roentgenologic manifestations of gastric cancer include departures from the normal contour, pyloric action, peristalsis, motility, flexibility, mobility, position, and size of the stomach. Enumerated in the order of their relative importance, these signs are:

1. Filling defects.
2. Alterations of pyloric function: (a) gaping of the pylorus, (b) obstruction of the pylorus.
3. Perversion of peristalsis: (a) absence of peristalsis from involved areas; (b) weak peristalsis; (c) antiperistalsis; (d) exaggerated peristalsis; (e) irregular peristalsis.
4. Altered motility: (a) rapid and early emptying (non-obstructive cases); (b) delayed emptying (obstructive cases).

5. Lessened flexibility.
6. Lessened mobility.
7. Altered size (capacity).
8. Displacement.

Filling Defects.—The filling defect is the basic radiologic sign of cancer and practically indispensable to a positive diagnosis. It is occasioned by the projection of the tumor into the barium-filled lumen of the stomach, thus producing irregularity of contour. At the stage at which most patients first come for examination, the tumor usually has attained considerable size, and the filling defect is sufficiently extensive to be readily seen.

In aspect, filling defects vary somewhat according to the character and seat of the neoplasm. The fungoid cancer often shows multiple gross irregularities, gradually shading off into the barium shadow, giving a more or less stereoscopic effect to the elevations and depressions.

The infiltrating scirrhus cancer may greatly, though somewhat irregularly, narrow the lumen of the affected portion, which is most commonly the pyloric end.

A small cancer at the pylorus may produce a broadening of the duodenopyloric hiatus or a conical vestibule. A more extensive cancer may seemingly cut off the entire prepyloric segment.

Cancer of the pars media may result in an hour-glass deformity. High up in the cardia the tumor may infringe upon the contour of the gas-bubble and contrast with the translucency of the latter.

A tumor on the anterior or posterior wall alters the contour in the sagittal view; in the anteroposterior view it may show centrally as a less dense area within the barium shadow.

The actuality and permanence of filling defects cannot be determined with finality by a few roentgenograms alone. Essential here is the screen examination, during which the gastric shadow can be studied at various angles by turning the patient and the effect of active and passive movements observed.

A true filling defect is permanent, showing no change in location or appearance after palpatory manipulation, after administration of antispasmodics, or upon reexamination.

Absence of peristalsis from the suspected area is highly confirmatory.

The correspondence of a filling defect to a palpable mass is strongly indicative of its genuineness.

Irregularity of outline and lack of symmetry are rather constant in true filling defects.

Filling defects in the pars media are less likely to be overlooked than those in the pars cardiaca or the pars pylorica. A filling defect high up in the cardia may not contrast strongly with the translucent gas-bubble. It may be brought into better relief by pressing the barium upward, or by screening and plating in the recumbent position. Small filling defects in the pars pylorica require careful study for detection, owing to the difficulty of obtaining a clear outline of this region, because of its proximity to the spine, and the tendency of the barium to settle away from the pylorus of a fish-hook stomach. A small defect, which may be well seen in the partly filled stomach, may be concealed in the distended stomach. Hence, observation should be made during the process of ingestion as well as after repletion. The diaphragm on the tube-box should be actively employed and the aperture narrowed to increase the distinctness of small suspected areas, thus facilitating close scrutiny. Filling defects situated in the pars media occasionally produce hour-glass deformity. More commonly such an hour-glass is of the X-type, in contradistinction to the usual B-type of gastric ulcer or gastric spasm, but this distinction is not invariable. As a rule, the hour-glass of cancer lacks the sharply defined contour of the hour-glass due to ulcer or spasm, and shows an indefinite shading off.

Filling Defects from Causes Other than Cancer.—Filling defects, either apparent or real, may be produced by numerous conditions other than cancer. Apparent filling defects may result from the use of faulty media (stiff media, poorly mixed or without sufficient barium); secretion in the stomach; food remnants; hair ball (trichobezoar); gas or fecal matter in the colon; barium in the bowel adjacent to the stomach; lordosis and scoliosis; pressure of the stomach against the spine; pressure of a deformed costal arch; strong retraction of the upper abdominal wall; spasm; adhesion

from perigastric inflammations; extrinsic tumors, including those of the liver, spleen, pancreas, kidney, large and small bowel, omentum, mesentery, and belly wall; displacement and distortion of the stomach by ascites, ovarian cysts, pregnancy, etc. Actual filling defects not distinguishable of themselves from those of cancer, may be caused by various benign tumor-producing lesions of the stomach.

Faulty media in which the barium is irregularly distributed may give varying degrees of opacity in the gastric shadow and thus imitate filling defects. The mixture may be too stiff, poorly mixed, or an insufficient quantity of barium may be used. With very thin mixtures the barium often settles to the lower pole, leaving irregular shadings along the lesser curvature. A little palpatory shifting of the gastric contents readily shows the character of these pseudo-defects, and erroneous interpretation is not likely to occur unless an attempt is made to base a diagnosis upon plates alone.

An excessive amount of secretion in the stomach, while it usually rises above the opaque meal, may mingle with it irregularly or thin its consistence. Sometimes secretion is imprisoned in the pyloric end of a fish-hook stomach, showing as a clear area above the opaque meal. The straight horizontal line of demarcation between the secretion and the barium is indicative of the artificial nature of the defect. By palpatory pressure the secretion can be displaced by the meal, or is passed into the duodenum.

Food masses in the stomach, by excluding the barium from the area in which they lie, may simulate filling defects. Here palpatory shifting of the gastric contents will cause the seeming defect to change its situation or disappear. However, as a matter of routine, patients should be examined only in the fasting condition. Employment of the tube to withdraw food remnants in cases of pyloric stenosis, unless otherwise contraindicated, may be resorted to if desirable.

Occasionally a hair ball (trichobezoar) is found in the stomachs of neurotic persons who are addicted to biting the hair. The accumulation may be a rounded ball, varying in size, or may form a complete cast of the gastric cavity. After giving the barium meal,

the stomach shows an area of diminished density somewhat like the filling defect produced by cancer on the anterior or posterior wall, the peripheral contour showing fairly well. If the ball is small, it can be displaced by manipulation or even forced up into the gas-bubble.

Gas in the colon is a common source of annoyance. Even after preparation of the patient by purging there may be more or less gas in the splenic flexure. Frequently the distention is sufficient to infringe upon the greater curvature and produce considerable irregularity. Such irregularities ought not to be very deceptive, as they change with manipulation, and the distention of the transparent loop of intestine is rather obvious. If the gas-bubble is intruded upon, the colonic haustra are usually evident. Occasionally the transverse colon may be displaced upward and lie directly across the stomach. Its course may be traced by its transparency and haustration. Fecal matter in the bowel might possibly cause indentations in the adjacent gastric contour, although we have never seen this condition.

Masses of barium from the six-hour meal, in the bowel adjacent to the stomach, sometimes produce apparent irregularities of the gastric contour on the plate. By the screen examination with changing positions and palpation their character is easily seen.

Deformities of the dorsal and lumbar spine, including lordosis and scoliosis, may deform the contiguous gastric contour. Such conditions are rather manifest and rare.

Pressure of the stomach against the spine, either normal or with well-marked physiologic lordosis, often disfigures the transspinal portion of the stomach. This disfigurement is often seen on the plates made with the patient's abdomen pressed tightly against the cassette. Not rarely it is also observed during roentgenoscopy, especially when the patient maintains a high degree of abdominal rigidity and tension.

Strong retraction of the belly wall sometimes occasions a wide, regularly curved depression in the greater curvature of the stomach, just below the left costal arch. Its smooth, sharp outline and its situation should differentiate it from an actual filling defect.

Spasm of the gastric musculature may produce very deceptive imitations of the filling defects caused by cancer. Migrating or intermittent spastic contractions, which are frequently seen, are evidently spasmodic because of their changing situation or interruption; but spasm is not always migratory or intermittent. Often a non-moving, spastic incisura will indent the stomach so as to form an hour-glass, exactly simulating an organic hour-glass stomach. In other cases the entire pyloric portion of the stomach may be constricted to a stiff, narrow tube, rolling under the palpating fingers as a cylindrical mass. Again, the entire stomach may be spastically contracted, small, and of finely irregular contour, without definite peristalsis. In all the above conditions the outline of the stomach, though not regular, is sharply defined, and this circumstance should put the observer on guard. However, there is still another variety of spasm which is dangerously misleading; in this form the barium shadow in the spastic area, which may be large or small, fades off toward the gastric periphery, exactly as though intruded upon by a tumor mass. The spasm may sometimes be effaced by massage during the screen examination, but reappears, as a rule. If accessible to palpation, the absence of a tumor from the suspected region should suggest cautious interpretation. The pyloric portion of the stomach is a common seat of this spastic deformity.

The points of difference between the true filling defects and those produced by spasm can be summed up as follows:

The true defect is permanent, may correspond to a palpable mass if accessible, and is not often sharply delineated.

The spastic filling defect is frequently migratory or transient, sharp in outline, and the contracted muscle is rarely palpable. Spasm may disappear upon distracting the attention of the nervous patient or by causing him to relax his abdomen, or by vigorous palpatory manipulation; or it may disappear or change its situation at a second examination. In a great many cases reëxamination after the administration of an antispasmodic is necessary. Belladonna, atropin, and papaverin are the drugs most generally employed. Commonly we give the tincture of belladonna in 15-

minim doses, three times a day, for two or three days or until the patient shows its effects. The procedure should never be omitted in any case in which the possible existence of spasm cannot absolutely be eliminated. In rare instances spasm may persist in spite of this measure, but such cases are quite uncommon.

Adhesions from perigastric inflammations may produce distortions and irregularities resembling the filling defects of cancer. The inflammatory process originates most commonly from perforating gastric ulcer or from pericholecystitis. A perforating gastric ulcer in the pars media producing perigastric adhesion is apt to reveal its identity by a pocket, a niche, or an incisura. Perforating ulcer in the pars pylorica may be less characteristic, but these cases have been quite rare in our experience.

Tumors extrinsic to the stomach may deform its contour. Such tumors may originate in the liver, spleen, pancreas, kidney, large or small bowel, omentum, mesentery, or belly wall. As a rule, the filling defect occasioned by their thrust into the gastric lumen is quite smoothly regular, the inequalities of the tumor being covered by the wall of the stomach. Unless adherent to the stomach, which is not usual, changes of position of the stomach with respiration or by palpation will alter the location of the filling defect. In these cases, also, the peristalsis is usually normal, and this fact speaks against a tumor of the stomach itself.

The stomach may be eccentrically distorted and displaced by ascites, ovarian cysts, and other large abdominal tumors, pregnancy, or even by a tensely retracted abdominal wall. Such conditions should be rather patent.

Intrinsic tumor-masses produced by syphilis and benign neoplasms, as well as varicosities of the gastric veins, may cause filling defects practically identical with cancer. These conditions are so unusual that the roentgenologist should not be unduly alert for them.

Alteration of Pyloric Function.—In cancer the pyloric function may be perverted in either one of two quite opposite ways: namely, either by gaping or by obstruction. The barium water often flows through a normal pylorus, with little or no interruption; but as

soon as the thicker pap is given the flow usually becomes scanty or intermittent. The gaping pylorus of cancer is characterized by a free and continuous exit of both mixtures into the intestine. Very commonly the stream is voluminous and the upper small bowel is speedily filled with the opaque mixture. The stomach may be almost or even completely emptied during the brief period of examination.

Gaping of the pylorus results from an interference with its sphincteric contraction, either by infiltration and stiffening of the muscular ring or by an absence of the pylorus-closing reflex. Thus it is seen quite typically in scirrhus cancer involving the pars pylorica, but it is also found in association with cancers of the cardia or media, either scirrhus or medullary. A free and continuous flow, somewhat similar to that seen with the gaping pylorus of cancer, may be found in other conditions, such as duodenal ulcer, gall-bladder disease (with or without adhesions), achylia, certain diarrheas, and sometimes even in chronic appendicitis. It should be said, however, that in these conditions the flow is less voluminous, as a rule, than that noted typically in cancer.

Pyloric obstruction, as evidenced by a six-hour residue in the stomach, occurs in about 60 per cent. of gastric cancers—oftener than with any other lesion. The amount of residue varies with the degree of obstruction. It is noteworthy that the lumen of the pyloric canal may be considerably diminished by the intrusion of a cancer without resulting in a six-hour residue, for the reason that the lessened caliber is compensated by the lack of sphincteric control. Since numerous causes other than cancer may operate to produce a six-hour gastric retention, the presence of a residue should not be given undue weight in making the final diagnosis, but its occurrence should stimulate a careful search for filling defects and other evidences of cancer.

Peristalsis.—The perversions of peristalsis resulting from gastric cancer are varied. Absence of peristalsis from a cancerous area of the gastric wall due to local loss of muscular contractility is a highly valuable sign. In some such instances a wave may progress to the affected site, skip it, and take up its course again beyond, and

this observation is one test for the genuineness of cancerous filling defects. Weak peristalsis, the waves being both shallow and infrequent, is fairly common in cancer. Frequently the stomach seems to be perfectly inert. Antiperistalsis is occasionally observed in cancer with pyloric obstruction. The antiperistaltic waves are best seen on the greater curvature in the pars pylorica and media. The waves are usually wide and shallow, though sometimes deep. Beginning at the pylorus, they sweep slowly backward and disappear in the upper media. They may coexist with peristaltic waves traveling in the normal direction. Exaggerated peristalsis, as a sequence of cancer with pyloric obstruction, is more rare than might reasonably be supposed. When seen, the exaggeration is usually more marked on the greater curvature. It may be irregular as to the depth and succession of the waves; a fairly deep wave may be closely followed by a shallow one, while the next may be normal as to depth and rhythm. None of the foregoing perversions of peristalsis are peculiar to cancer, and they are merely indicative of a pathologic process.

Altered Motility.—Emptying of the cancerous stomach may be either retarded or accelerated, according to the presence or absence of pyloric obstruction. In the non-obstructive cases hypermotility is the rule, and is a natural sequence of the achylia and gaping pylorus. The acceleration of gastric clearance may be extreme and the stomach evacuate itself with extraordinary rapidity. The acceleration is often exhibited not only in a rapid and early clearance of the stomach, but also in an advanced position of the six-hour meal, the head of the barium column appearing in the transverse colon, the splenic flexure, the descending colon, or even the ampulla. In the obstructive cases, delayed clearance is shown by the six-hour residue. The portion of the meal which has passed through into the intestine may or may not show retarded progress. It is to be remembered that gastric motility may be affected by many things other than cancer. Hypermotility of moderate degree is a common sequence of non-obstructive duodenal ulcer, achylia, and diarrhetic conditions. Hypomotility, with or without a six-

hour retention, may result from any sort of organic obstruction at the pylorus or near beyond, or from reflex pylorospasm.

Lessened Mobility.—By involving adjacent structures a cancer not infrequently produces more or less fixation of the stomach. The attachment may be to the abdominal wall, or to the liver, pancreas, or other viscera. The presence of fixation may sometimes, but not always, be determined by palpatory maneuvers, depending upon the position of the stomach, the situation of the attachment, and the degree of laxity of the abdominal wall and also by observation during forced respiration. The small, high-lying, contracted stomach, inaccessible to manipulation, though it appears to be fixed, is not necessarily so. On the other hand, a stomach which has a free and flexible lower pole may seem to be freely mobile, when there are definite adhesions on the lesser curvature. Inasmuch as fixation is simply an indication of extragastric involvement, it is merely a contributory sign of cancer. It may be taken into account in estimating the possibility of resection.

Lessened Flexibility.—Diminished flexibility of the cancerous gastric wall is a practicable and valuable sign, especially of scirrhus cancer. Upon narrow palpation with a single finger or with the ulnar edge of the hand the accessible normal gastric wall will show corresponding indentation, whereas if stiffened by infiltration it will either be disproportionately indented or be moved aside *en masse*. The loss of pliability may also be somewhat evident by the lack of change of contour during deep respiration or during variations of abdominal tension. Further, it may show as a lack of expansibility in the affected portion during the process of filling the stomach, the lumen of the involved area being almost constant in size at all degrees of repletion, while the unaffected portion expands to accommodate the increased volume.

Altered Size and Capacity.—A common feature of the cancerous stomach is marked diminution of the capacity and apparent size. The reduction may be the result either of the projection of large fungoid masses into its lumen or the shrinking effect of scirrhus infiltration. In extreme instances the effort to accommodate the ingesta causes a backing up of the meal in the esophagus,

which latter may show dilatation. Besides cancer, other causes which may lessen the capacity of the stomach are perforating ulcer, with extensive perigastritis, spasm, and benign lesions. The upper loculus of an hour-glass stomach may be mistaken for a contracted stomach if the presence of the lower loculus be overlooked. It must also be remembered, on the other hand, that an obstructive cancer at the pyloric end may result in considerable dilatation of the stomach. A similar dilatation may be consequent upon other obstructive causes. It follows then that neither large nor small size of the stomach is especially significant of cancer, but marked variation in size of the stomach is at least suggestive of the presence of a lesion.

Displacement.—The predilection of cancer for the pyloric end of the stomach, often with more or less complete obliteration of the distal portion of its lumen, results frequently in an apparent displacement of the stomach to the left, since its proximal portion only is visualized. Aside from this, however, there may be actual displacement upward and to the left in cases of scirrhus cancer, and the diminished organ may lie entirely up under the shelter of the left costal arch. Somewhat similar displacements may occur as a result of perforating ulcer, ascites, tumors outside the stomach, and retraction of the abdominal wall.

PATHOLOGY

With the microscopic pathology of gastric cancer the roentgenologist has little concern, but the roentgenologic appearances of cancer sometimes depend quite considerably upon its character as affecting its form, location, and extent. Hence, a few statements concerning certain anatomic varieties of cancers and their gross aspects may assist in clarifying the description of this lesion, as seen by the roentgen rays.

Cancers of the stomach invariably originate in the mucous layer. While they are all basically epithelial neoplasms, they present numerous structural differences. Disregarding those variations which are here unimportant, there are three forms which are of chief interest from a radiologic standpoint:

1. A proliferative form, almost wholly epithelioid in composition, with circumscribed tumor-production. This is the *fungous* type with which may be included, for present convenience, the medullary (encephaloid), cauliflower, and adenocarcinomas. It is characterized by a relatively small amount of interstitial tissue, and hence is soft.

2. An infiltrative form. This is the *scirrhus* type. Speaking in a general way, it infiltrates the gastric wall with less unevenness and less projection into the cavity of the stomach than are seen in the fungous type. It is characterized by a relatively large amount of interstitial tissue, is hard, and is more frequently associated with ulceration than the other types. The infiltration may be either (a) localized or (b) general.

(a) When localized, the pyloric end of the stomach or the lesser curvature is the part most commonly affected, the greater curvature being rarely involved at the beginning.

(b) The general diffuse infiltration involves a large part or the whole of the stomach, which is thick-walled and contracted. This is regarded by many as identical with the so-called "leather-bottle" stomach, or "diffuse fibrosis," and is rather rarely seen.

3. A degenerative form, the so-called "colloid" or, more correctly, mucoid cancer. In this form the cells lose their structure and become merged into a homogeneous mucoid mass. Mucoid degeneration may occur in either the fungous or scirrhus type.

It will be understood that the three forms mentioned do not always or necessarily exist independently of each other, that the classification and descriptions are practical rather than accurate, and that differentiation of these forms is not always easy. Sometimes these pathologic differences in gastric cancers are sufficiently manifest in the roentgenologic picture to warrant an opinion as to their probable nature; however, such an opinion should be advanced with caution, and then only in those rather few cases which are typical, for, in the majority of cases, the roentgenologist would better be content with a diagnosis of cancer without attempting to specify the particular variety.

Roentgen Characteristics of Fungous Cancer.—In a broad way

the typical fungous (medullary, encephaloid) cancer shows the following:

1. A non-shrinking effect upon the stomach as a whole. While the capacity of the stomach may be somewhat lessened by the encroachment of the mass upon its lumen, the gastric dimensions are not otherwise diminished. Often the hook form is preserved, and this retention of the hook form has been suggested by Haudek as an indication of resectability.

2. Occasional involvement of the greater curvature, especially of the body of the stomach.

3. Sharp delimitation of the involved from the non-involved portion of the gastric wall.

4. Often large, multiple, irregular filling defects projecting into the gastric lumen and shading gradually into the central barium shadow, somewhat resembling impressions upon paraffin.

5. If at the pyloric end, this type is likely to produce obstruction.

Roentgen Characteristics of Scirrhus Cancer.—Typical advanced scirrhus cancer may be recognized by:

1. Its marked shrinking effect upon the stomach. The capacity of the stomach is not merely lessened by a filling defect, but is greatly diminished by the loss of expansibility due to wide-spread infiltration as well as actual contraction.

2. Frequent involvement of the pyloric end and lesser curvature. Quite commonly a scirrhous completely encircles the pyloric end, and the deformity thus produced gives the stomach some resemblance to a curved funnel or an Indian pipe. The barium projects into the canalized pyloric mass as a smooth or slightly irregular spicule.

3. Gradual merging of involved into non-involved portion of the gastric wall. The limits of the lesion are difficult or impossible to determine radiologically. The lesion is usually more extensive than the picture indicates.

4. The filling defects of scirrhus cancer are commonly less grossly irregular than those of the fungous type.

5. This type of cancer, even though involving the pars pylorica, is likely to show a gaping pylorus.

Mucoid Cancer.—A markedly diminished, fairly regular central lumen surrounded by a thick-walled tumor mass is sometimes seen in extensive mucoid degeneration, but mucoid change can rarely even be surmised by the radiologic appearances. It gives practically the same screen and plate picture as the infiltrative form (scirrhus).

Carcinomatous Ulcer.—While by far the greater number of gastric cancers manifest themselves frankly as tumors at the time the patients present themselves for examination, ulcers are found occasionally which show microscopic evidence of malignancy. In their gross characteristics and roentgenologic appearances these ulcers are not different from benign ulcers. In most instances the crater of the ulcer is visualized as a niche projecting from the gastric lumen. This may or may not be associated with hour-glass stomach, an incisura, or six-hour retention. The only suspicious feature sometimes shown by the roentgen rays is the extraordinarily large size of the ulcer crater. In a few of our own cases, in which the niche was 3 or 4 cm. broad, the ulcer was found on microscopic examination to be malignant.

OPERABILITY

In deciding the question of operation in a given case of cancer the roentgen rays furnish information of high, often decisive, importance. Primarily, operability depends considerably upon the skill of the operating surgeon; but aside from this, certain radiologic findings speak for or against operation, whether radical or palliative. The location, extent, and character of the cancer are all matters of fundamental weight. Growths involving the cardia or upper media are not accessible to resection, while those at the pyloric end or lower media are often resectable. Obviously, resectability depends also upon the extent of involvement, and this can be more nearly determined by the roentgen rays than by any other method. The actual extent of a medullary cancer corresponds closely to that indicated radiologically. The limits of a scirrhus cancer are much less sharply defined in the

roentgen picture, and a liberal allowance must be made in estimating the probable degree of involvement.

Free mobility of a cancerous stomach is an item favoring resectability, while marked fixation resulting from extension to adjacent structures makes successful intervention less probable. However, a cancer which does not extensively involve the stomach or appear to have lessened its mobility materially may at operation be found to have invaded and be adherent to a near-lying organ, such as the pancreas, and resection of the growth is impossible.

Retention of the hook form of the stomach, which has been advanced as an indication of resectability, is often found in cases that are manifestly inoperable.

Regarding metastasis, a factor which has always to be considered, the roentgen examination can rarely give any information. Extensive metastasis in the lungs may be observed casually during the screen examination, or an abnormally large shadow of the liver may be a suspicious circumstance, and these should always be looked for; but wide-spread glandular metastasis may exist without detection.

Years ago, Czerny³ pronounced cases of cancer with definite palpable tumors of the stomach to be inoperable. This is rather extravagant, since many such cancers are resectable, and when there is no glandular involvement or invasion of adjacent tissue, the chance for cure is good. Further, not every palpable tumor is a cancer; the mass may be a perforating ulcer with adhesions, pancreatic cyst, floating spleen, or various lesions originating in the gall-bladder.

On the clinical side, the evidences of inoperability have been summed up by W. J. Mayo⁴ as follows:

"1. The cachectic patient with marked evidence of progressive gastric trouble which has lasted over a period of a number of months, with a fixed tumor lying to the left. Such a case would be clearly hopeless.

"2. It frequently happens that with cancer of any of the abdominal viscera there will be an escape of cancer cells into the peritoneal cavity. These will drop, by gravity, to the bottom of

the pelvis and become attached often to the sigmoid. The "feel" of these various small metastases upon rectal examination is very characteristic. In women, not infrequently transplantation to the ovary occurs, setting up a secondary malignant cyst. The majority of cases of malignant adenocarcinomas of both ovaries have such origin, and women are sometimes unnecessarily submitted to operation for their removal.

"3. The supraclavicular fossa, especially the left side, should be examined for carcinomatous glands.

"4. Cancer cells free in the abdominal cavity can be carried by the lymphatics to the umbilicus, forming a distinct mass like a button. In doubtful cases I remove, under local anesthesia, a little portion of this "button umbilicus" for microscopic examination.

"5. Metastatic deposits, giving rise to nodular tumors in the liver or peritoneal cavity.

"6. Ascitic accumulations in the abdominal cavity, taken in connection with the history of the patient, have some value. It is necessary to eliminate other causes of ascites—for example, the heart, liver, kidneys, tuberculous peritonitis, etc."

Roentgenologic determination of the absence or presence of obstruction, its site and degree, aids materially in judging the advisability of palliative surgery and in selecting the operation, whether gastro-enterostomy, gastrostomy, or jejunostomy. In expressing any opinion as to operability, unless the cardia or upper media is definitely implicated, or unless the growth is extraordinarily extensive, the roentgenologist should be chary of saying that a case is inoperable, as he may thus deprive the patient of relief or cure at the hands of the surgeon. In the majority of instances exploration alone is the final word, and the patient should be given the benefit of the doubt. Besides, there is always at least a remote chance that the most confident diagnosis may be wrong.

EARLY CANCER

The term "latent cancer" is sometimes applied to cancers which give rise to few or no symptoms or signs and which cannot be diagnosed clinically. Since "latent" also carries the

sense of quiescence or dormancy, a condition which has not been proved as regards gastric cancer, the adjective "early" is perhaps preferable.

Admitting that the only cure for cancer is early operation, early diagnosis is a matter of prime importance. Admitting also that there are no definite clinical findings in early cancer, the statement is warranted that next to the exploring finger of a trained surgeon, roentgen rays will reveal more cancers in the early stages than will any other diagnostic means. Hence every patient of cancer age with indefinite gastric symptoms should be subjected to a roentgen examination. But how early can cancer of the stomach be detected? That depends upon:

1. The character of the cancer, whether a frank tumor, an insidious infiltration, or a cancerous ulcer.
2. Its situation.
3. The examiner's familiarity with the work.
4. The amount of roentgenologic evidence, together with the extent of clinical corroboration.

Cancer which begins candidly as a tumor projecting into the gastric lumen is susceptible of quite early recognition by reason of the filling defect which it produces. The test of this sign is its permanence, not its size, and we have been fortunate enough to find one which was not larger than a cherry. The discovery of even smaller ones is no doubt possible. A stealthy infiltrative cancer of the fibrous or scirrhous type may invade the gastric wall without producing a recognizable filling defect. In this event peristalsis should be notably absent from the involved area, and a local loss of flexibility may be evident upon palpation. When these signs alone exist, they should be interpreted with caution; but in conjunction with a gaping pylorus, achylia, and clinical indices, they may warrant a surgical exploration.

Carcinomatous ulcers for the most part show the same roentgenologic signs as simple ulcers. However, as stated, ulcers with excessively large craters are open to the suspicion of being cancerous.

The situation of a small cancer makes a decided difference in the chance of its demonstration. On either curvature of the pars media

or pars pylorica, filling defects, even though small, can usually be visualized on the screen or plate, or both; but such defects on the anterior or posterior wall might evade observation even in the oblique view. Trifling defects in the region of the gas-bubble are also apt to be overlooked. The percentage of cancers in the pars cardiaca is, however, small.

The experience of the examiner and his ability to see and interpret slight departures from the normal have some importance in the diagnosis of early cancers. The novice would better limit his diagnoses to those cases in which he can demonstrate a permanent filling defect, and which are at least suspicious clinically. These features will be found in the vast majority of patients with gastric cancer who seek medical aid.

Patients with early cancer near the pyloric ring producing obstruction are more likely to come into the hands of the roentgenologist than patients with early cancer beginning elsewhere in the stomach. A six-hour retention, evidencing obstruction, may be the only abnormality of which the observer feels sure. In other cases there may be slight but permanent irregularity of the prepyloric contour, with or without obstruction, in which one can only say with certainty that a lesion of some sort is present. While it is highly important that gastric cancers be discovered at the earliest possible moment, it is also highly important that the diagnosis shall be well founded, and where the roentgen findings plus the clinical features of the case do not quite justify operative intervention, the patient should be reëxamined at short intervals until a decision is reached. The administration of belladonna to eliminate the possibility of spasm in doubtful cases is particularly advisable.

INTERPRETING THE SIGNS OF CANCER

The roentgen indications of gastric cancer vary markedly in degree and in their combinations with each other, as will be seen in the case reports herewith appended. The cases with which the roentgenologist has to deal thus range all the way from those which are plainly cancer to those which are highly doubtful. Often he can only be positive that a

pathologic condition exists. In every case he should be acquainted with the salient clinical facts, which should at least grossly correspond to his own findings. If they do not agree, he ought to confirm his observations by repeated examinations.

CASE 97,408.—Man, aged forty-three years. He had attacks of indigestion five years prior to examination, with slight pyrosis and vomiting, which ceased after medical treatment. For five weeks he had been having spells of sharp epigastric pain, relieved by rest and



Fig. 46.

aggravated by exercise. No loss of weight. Hemoglobin, 89. Total acids, 86; free HCl, 62; combined, 14; no food remnants. *Roentgen findings:* Small prepyloric filling defect. Retention of half the six-hour meal. Active peristalsis (Fig. 46). *Diagnosis:* Lesion at the pylorus. *Operation:* Resection four inches of stomach (Billroth No. 1); early cancer on pyloric ulcer. *Pathologist's report:* Ulcer, early cancer.

It will be noted in the patient's history that the symptoms complained of were indefinite and not especially indicative of cancer.

Such an early lesion could hardly have been discovered except by roentgen rays or by exploration. This is a typical early case, in which good results can be expected from operation.

CASE 90,713.—Man, aged sixty-seven years. Four months ago the symptoms began, with belching and regurgitation of sour, foul-smelling water a half to one hour after meals. There was



Fig. 47.

sticking, heavy, left epigastric pain soon after eating. Loss of weight, 15 to 20 pounds. Total acids, 56; free HCl, 42; combined, 14; food remnants; blood. Epigastric resistance and tenderness, but no mass palpable. *Roentgen finding*: Small filling defect, pyloric end. No palpable mass corresponding to defect. Retention of three-fourths of the six-hour meal. Somach large, showing irregular, vigorous peristalsis (Figs. 47 and 48). Fig. 48 shows



Fig. 48.



Fig. 49.

the retention after six hours. *Diagnosis:* Carcinoma, pyloric end. *Operation:* Cancer in the pyloric end of stomach, ulcer type, with marked obstruction. Adherent to pancreas. Extensive glandular involvement. Resection of one-half of the stomach (Mikulicz-Hartmann-Billroth No. 2). *Pathologist's report:* Cancer. Photographs of gross specimen shown in Fig. 49.

While this is a fairly early case roentgenologically, as shown by the limited involvement of the stomach, the surgical findings prove that even small cancers of the stomach are not always favorable



Fig. 50.

for resection, because of extension to adjacent tissues and glandular involvement.

CASE 122,965.—Man, aged thirty-six years. This patient had had indigestion off and on for ten years. Onset of present trouble two months ago. Distress, gas, and nausea three or four hours after taking food, with regurgitation of acid and mucus. Loss of weight, 8 pounds. Movable ridge at right epigastrium. Total acids, 40; free HCl, 0; combined, 40; food remnants, 2; blood, yeasts, sarcinæ. *Roentgen findings:* Large stomach, con-

'15—10

taining three-fourths of the six-hour meal. Filling defect in the pars pylorica corresponding to a palpable mass (Fig. 50). *Diagnosis:* Cancer, operable so far as the extent of the involvement of the stomach is concerned. *Operation:* Resection of two-thirds of the stomach (Mikulicz-Hartmann-Polya). Cancer, pyloric end. *Pathologist's report:* Cancer with glandular involvement.

This patient had slight gastric disturbance for ten years, as stated above, and had been seen repeatedly by competent gastroenterologists, one of whom sent him to Europe for a vacation trip. Another sent him to Florida last winter. He had had roentgen examination by one or two inexperienced men, who were also practising internal medicine. The case was not recognized as cancer until a tumor developed. A careful roentgen examination should have shown the condition earlier and at a time more favorable for operation.

CASE 123,461.—Woman, aged fifty-one years. For five years before coming for examination this patient had had intermittent attacks of epigastric pain two hours after taking food, lasting weeks or months, with intermissions of two to six months. For five months she has been vomiting whenever she ate a little more than usual, and during the past two months she has had epigastric pain immediately after taking food, and at other times. Loss of weight, 28 pounds in five months. Small, movable, tender mass in epigastrium. Hemoglobin, 85. Total acids, 20, all combined. *Roentgen findings:* Extensive filling defect involving both curvatures, extending well up into cardia, corresponding to palpable mass. No six-hour retention. Gaping pylorus (Fig. 51). *Diagnosis:* Inoperable cancer. No operation.

If this patient had been examined by roentgen rays only a few months earlier, there is little doubt that a diagnosis could have been made when surgery could offer some hope of cure.

CASE 86,914.—Man, aged sixty-one years. From the age of eighteen to forty-two he had attacks lasting three to five weeks once a year, of epigastric pain an hour or two after taking food, with sour regurgitation, etc. One month ago he had an attack of pain with vomiting, followed by fermentation and distress. Five days later at his home exploratory operation showed tumor of the stomach, which was not removed. Loss of weight, 26 pounds. Total acids, 54; free HCl, 4; combined, 50. Large, movable ridge in epigastrium. *Roentgen findings:* Stomach small, with marked filling defect in the pars media and pars pylorica, corresponding to a pal-

pable mass. Retention of half the six-hour meal. Stomach somewhat fixed (Fig. 52). *Diagnosis:* Cancer. *Exploration:* Cancer of the pyloric end of the stomach; inoperable. *Pathologist's report:* Tissue removed, cancer.

This case shows how impossible it is to accomplish anything by surgery when such an advanced stage of the disease has been reached. The roentgen rays were not at all necessary for a diagnosis in this case, but showed the extent of involvement and its



Fig. 51.

inoperability. Only by competent routine roentgen examination of every person beyond cancer age with gastric symptoms, no matter how trivial, can the number of cases like the above be diminished.

CASE 117,798.—Woman, aged sixty-six years. In the past five years this patient has had many attacks of grinding pain in the right abdomen, coming suddenly and lasting from a few to twelve hours. For four months she has had daily distress and sour vomiting soon after meals. Loss of weight, 30 pounds. Hemoglobin, 85. Total acids, 24; free HCl, 16; combined, 8. *Roentgen find-*

ings: Prepyloric narrowing. Retention of half the six-hour meal. Active peristalsis. Some irregularity and thinning of barium shadow along the greater curvature in the pars media, due to gas in the colon (Fig. 53). The case was regarded as suspicious for a prepyloric lesion. A reray after belladonna was requested, and this examination showed a stomach normal in contour and without retention. *Operation:* Cholecystectomy; appendectomy. Cholecystitis with multiple papillomas; chronic appendicitis. *Pathologist's report:* Chronic cholecystitis with multiple papillomas. Chronic appendicitis.



Fig. 52.

This case illustrates the necessity of caution on the part of the radiographer. The prepyloric deformity and six-hour retention were due to gastropasm as a reflex from the disease of the gallbladder. This sort of gastropasm is of quite common occurrence, and extreme care is necessary in differentiating it from an actual lesion of the stomach. The active peristalsis in this instance rather suggested spasm and negated cancer.

CASE 102,013.—Woman, aged sixty-nine years. Two years ago this patient began to have discomfort after meals. A year later

she noticed a lump in the epigastrium which has increased steadily in size. During the past eight months occasionally she has been nauseated and vomited when hungry. Loss of weight, 45 pounds. Hemoglobin, 85. Total acids, 6, all combined. Oblong mass in epigastrium. *Roentgen findings:* Small stomach without visible peristalsis. No retention. Lessened flexibility. Slight fixation. Lumen narrowed without marked irregularity of contour (Fig. 54).



Fig. 53.

Diagnosis: Cancer. *Exploration:* Inoperable tumor involving the entire stomach (leather-bottle stomach). Some glandular thickening, but no metastasis.

CASE 124,629.—Man, aged forty-four years. Eight months ago he began to have epigastric pain, coming a half-hour to one hour after meals. The pain continued until about six weeks ago; since then he has felt well, but worries over loss in weight (15 pounds). A firm tumor could be palpated to the left of the umbili-

cus, indefinite in outline, moving with respiration, and visibly modified in shape, evidently by peristalsis. Total acids, 66; free HCl, 60; combined, 6. *Roentgen findings:* Extensive filling defects in the pars media and pars pylorica. No retention from the six-hour meal (Fig. 55). *Operation:* Resection of three-fourths of the stomach (Mikulicz-Hartmann-Polya). Cancer, two large masses projecting from the posterior wall. *Pathologist's report:* Cancer; no glandular involvement found.

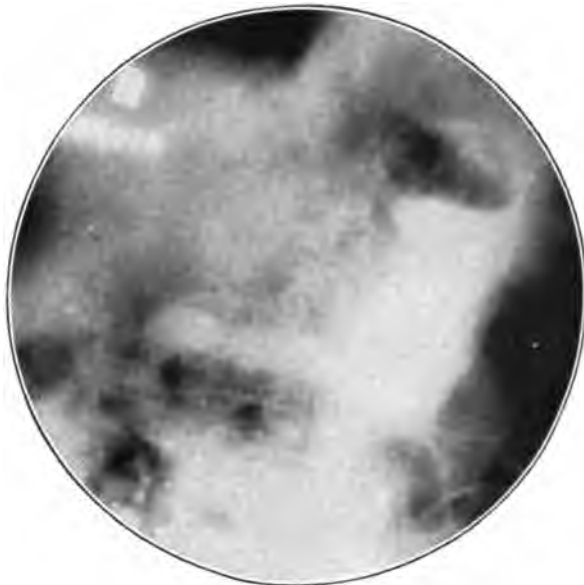


Fig. 54.

CASE 119,622.—Woman, aged sixty years. For several years the patient has had, every five or six months, attacks of nausea and vomiting, without pain, lasting about a week. A similar attack began one month ago, at first without relation to food-taking, but during the past two weeks occurring a half to three hours after meals. No particular pain, but some epigastric soreness and burning. Loss of weight, 38 pounds in two years; mostly in the past two months. Hemoglobin, 76 per cent. Ridge in the left epigastrium palpable on deep inspiration. *Roentgen findings:* Very large niche on lesser curvature. Retention of half the six-hour meal (Fig. 56). *Diagnosis:* Cancerous ulcer. (The opinion as to malig-

nancy was based upon the unusually large size of the niche.) No operation.

CASE 106,071.—Woman, aged fifty-five years. For twenty years she has had attacks of severe epigastric, cramp-like pain, coming as often as every two weeks, lasting one or two hours, and without relation to food. For six months attacks have been more frequent; recently twice a day. Morphin for relief has been given.



Fig. 55.

Vomiting of dark greenish fluid. Small, tender mass in the right costal margin. Loss of weight, 25 pounds. Hemoglobin, 85. Total acids, 40; free HCl, 28; combined, 12. *Roentgen findings:* Two examinations were made. The first showed marked irregularity of the pyloric end, without retention. The second examination, after giving belladonna, showed practically the same condition (Fig. 57). *Diagnosis:* "Prepyloric irregularity; possible lesion; may be reflex." *Operation:* Cholecystectomy. Empyema

of gall-bladder with stones. *Pathologist's report:* Cholecystitis. Cholelithiasis.

The cautious diagnosis in this instance was due to the fact that the patient had an excellent history of gall-bladder trouble. The patient at the second examination showed no physiologic effects from the belladonna, and it was felt that spasm could still not be wholly excluded. Further, an organic lesion of the stomach producing such prepyloric irregularity would probably also have



Fig. 56.

resulted in a six-hour retention, antiperistalsis, palpable tumor, or other corroborative indication.

CASE 106,124.—Man, aged seventy years. Intermittent diarrhea for six months, with three to six bowel movements daily. Occasional day or two of relief. Much sour belching. On rigid diet five months, with 40 pounds loss of weight. Occasional pain in the lower abdomen or stomach. Hemoglobin, 75. Total acids, 14, all combined. Stool report: No parasites. Proctoscopic nega-



Fig. 57.

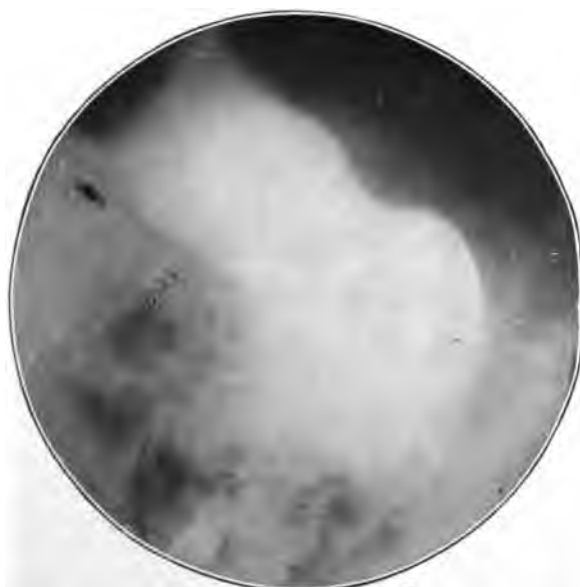


Fig. 58.

tive. *Roentgen findings:* Filling defect in the pars pylorica. No six-hour retention (Fig. 58). *Diagnosis:* Cancer. *Operation:* Cholecystectomy. Large septic gall-bladder, with stones. Marked thickening of pyloric ring by spasm. *Pathologist's report:* Chronic catarrhal cholecystitis. Cholelithiasis.

Because of the patient's age and weakness the examination was effected with considerable difficulty. The findings, however, seemed quite definite, and the possibility of spasm was not considered. The clinicians in charge of the case had considered it disease of the



Fig. 59.

gall-bladder, but upon the strength of the roentgen-ray findings changed their diagnosis. The case is another illustration of the deceptiveness of gastrosplasm.

CASE 120,996. — Man, aged fifty years. Two or three months ago he began to have intermittent attacks of dull epigastric pain one hour before meals, lasting three or four days, with remissions of four or five days. Food relief. Some pyrosis, pallor. Slight edema of feet and legs for three or four weeks. No distinct loss of weight. Mass, right hypochondrium. Total acids, 10; free

HCl, 0; combined, 10; blood and mucus. Hemoglobin, 40, *Roentgen findings*: Plates made with the patient standing show small defect on the greater curvature in the pars media, while those made prone show two large central defects; with some irregularity and thinning of both curvatures. No retention from the six-hour meal (Fig. 59). *Diagnosis*: Cancer. *Operative findings*: Anterior gastro-enterostomy; stomach opened; base of tumors clamped. Four cancerous papillomas growing from the mucosa of the stomach, varying in size from that of a filbert to that of a lemon. *Pathologist's report*: Multiple papillomas; areas of cancer.

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GASTROJEJUNAL ULCERS—THEIR ROENT- GENOLOGIC AND SURGICAL ASPECTS *

RUSSELL D. CARMAN AND DONALD C. BALFOUR

Gastro-enterostomy for a definite lesion, such as gastric or duodenal ulcer, is followed exceptionally, after a variable period of relief, by a recurrence of symptoms. These symptoms are unrelieved by medication, and are often similar to those produced by the original lesion. Without discussing other possible causes, we wish to emphasize the fact that occasionally the disappointing result is due to the development of another ulcer in the vicinity of the gastro-enterostomy. These ulcers have been variously described as gastrojejunal and jejunal ulcers, and it is quite probable that cases of jejunal ulcer have been reported which were essentially gastrojejunal, and vice versa. Thus in reviewing the literature one is confronted with considerable difficulty in selecting cases of undoubted gastrojejunal ulcer.

Paterson¹ was one of the first to draw attention to these ulcers, and his comprehensive article refers to 51 other cases collected from the literature up to that time, 14 of which were apparently true gastrojejunal ulcers. Other cases have been reported by W. J. Mayo,² Moynihan and Tatlow,³ Mayo-Robson,⁴ and Soresi.⁵ From the records of our Clinic we have been able to collect 13 cases not hitherto reported. The salient facts of these are shown in Tables I and II.

A study of this group of 13 cases does not enable us to state any symptoms or group of symptoms, or any physical findings which

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TABLE I.—CLINICAL DATA PRIOR TO SECOND OPERATION

CASE NUMBER	PERIOD BETWEEN FIRST AND SECOND OPERATIONS	PERIOD FREE FROM SYMPTOMS	ONSET OF SYMPTOMS	RELATION OF PAIN TO FOOD	LOCATION OF PAIN	RELIEF OF PAIN		VOM- ITING	CHARACTER OF VOMITUS	FOOD RETEN- TION	TUMOR
						Food	Soda				
12,969...	Yr. Mo. Day 4 10 11	5 years	Gradual, daily, past six months	Irregular	Epigastrium	0	0	+	Bitter slime	0	0
69,645...	8 14	3 months	Gradual	?	?	0	+	0	0	++	0
76,664...	10 13	6 months	Sudden and severe	Increased by food	Left lower abdo- men	0	0	+++	Sour, bitter	++	0
101,545...	16	complete	Weekly for years, con- stant one year	?	Right iliac fossa	0	0	++	Retained food	+	+
81,906...	11 23	1 month	Gradual	0	Epigastrium	0	?	0	0	0	0
115,555*	8 2 27	1 year	Gradual	Increased by solid food	Epigastrium, lower left abdo- men	0	0	++	Food remnants	+++	At second oper- ation +
98,687...	1 1	3 months	Gradual	After meals	Epigastrium	0	+	0	0	++	0
83,614...	1 5 5	2 months	Gradual	3 hours after meals	To right of, and below umbilicus	+	0	0	0	0	+
98,939...	10 17	3 months	Gradual	Soon after taking food	Left of umbilicus	+	+	0	0	0	0
50,276...	3 3	1 year	Intermittent, spring and fall	10 to 12 p. m.	Epigastrium	+	+	+	Sour water	+	+
101,624...	1 21	?	Gradual	3 hours after tak- ing food	?	Milk	0	0	0	0	0
131,378...	3 21	?	Gradual	3 hours after tak- ing food	Epigastrium	+	0	+	?	0	0
51,115...	10 29	3 months	Gradual	2 to 4 hours after taking food	Left hypochondrium	+	+	+	Sour	0	At second oper- ation +

* Period between second and third operations, 5 months, 22 days

could be considered pathognomonic of these secondary ulcers. However, it is rather suggestive of a gastrojejunal ulcer if the patient complains of pain, of the same character, relationship to meals, and severity, as in the previous trouble, though in a different situation—usually to the left of the midline and below the umbilicus.

Assistance from the roentgen ray might reasonably be expected in the diagnosis of this condition, although, so far as we are able to learn, gastrojejunal ulcer has received little attention from the roentgenologic point of view. Mathieu and Savignac⁶ note that, in cases of jejunal ulcer perforating the colon, the roentgen rays will show direct passage of bismuth into the colon. They state further that the colon may be narrowed by adhesions in the vicinity of the fistula, and the small intestine may be dilated in all or in parts of its length. These conditions are also susceptible of demonstration by roentgenoscopy. Their remarks seem to be based largely on some cases reported by Lion and Moreau,⁷ who collected five cases of jejunocolic fistula, including two of their own. One of these was examined with the roentgen ray by Bécélère.

Moynihan and Tatlow's³ case of gastrojejunal ulcer was rayed by Rowden, but his report was non-committal. Barsony⁸ reports a case of gastrojejunal ulcer in which the roentgen ray showed a pocket at the line of anastomosis the size of a kroner. Some five hours later the pocket was still filled with bismuth after the stomach was empty. Barsony lays strong emphasis on the persistence of bismuth in the ulcer cavity as being characteristic. But, excepting one of the cases hereinafter reported (see Fig. 66), we have not noted any roentgenologic evidence of a cavity resembling the niche of penetrating gastric ulcer or the accessory pocket of perforating ulcer. The nature of the ulcer rather precludes any probability of visualizing its crater as a niche; for the reason that the ulcer is most often characterized by surface area rather than depth, like many of the saddle-ulcers of the lesser curvature.

Nevertheless, nearly all the cases in our series showed abnormalities not customarily seen in the gastro-enterostomized stomach. After gastro-enterostomy the following conditions are found normally:

1. The opaque meal passes freely through the stoma. This is the rule, subject to occasional exceptions, even after the lapse of years.

2. No retention is present in the stomach from the six-hour meal.

3. The duodenum is not dilated.

4. The stomach is usually small.

5. Peristalsis is not overactive.

6. The gastric contour in the vicinity of the stoma is not usually deformed, save for a slight dimpling at that point occasionally.

7. The efferent limb of the jejunum is neither narrowed nor markedly irregular in outline.

8. Extensive adhesions about the stoma simply as a result of operation are uncommon, and the stomach is at least moderately mobile.

9. The stomach is not deformed (unless by the original lesion or its resection) and has no tendency to hour-glass form or spasticity.

Eleven of our 13 patients were subjected to roentgenoscopy, with the following results:

CASE 12,869.—First operation August 1, 1908; posterior gastro-enterostomy for perforating duodenal ulcer. Roentgenoscopy, June 6, 1913, showed the gastro-enterostomy moderately patent. A filling defect was noted in the greater curvature, pars media, at the site of the stoma. There was no retention from the six-hour meal. The stomach was of average size and peristalsis was normal. No barium was seen passing pylorus at the time of the examination.

CASE 69,645.—First operation October 10, 1912; posterior gastro-enterostomy for calloused duodenal ulcer. Roentgenoscopy, June 14, 1913, showed the gastro-enterostomy patent but not freely so. Some irregularity of the stoma was not well shown in the plate. The stomach was slightly larger than the average gastro-enterostomized stomach; it was freely mobile, showing normal peristalsis. The duodenal bulb was irregular; the pylorus was free (Fig. 60).

CASE 76,684.—First operation December 5, 1912; posterior gastro-enterostomy for perforating duodenal ulcer. Roentgenos-

copy, October 5, 1913, showed no retention from the six-hour meal. The stomach was larger than the average; its mobility was lessened. There was hyperperistalsis. The gastro-enterostomy was not freely patent. A marked filling defect was present on the greater curvature about the stoma. Barium in considerable quantity could be pressed through pylorus. The bulb was irregular.

CASE 81,306.—First operation March 24, 1913; posterior gastro-enterostomy for large posterior duodenal ulcer with contact

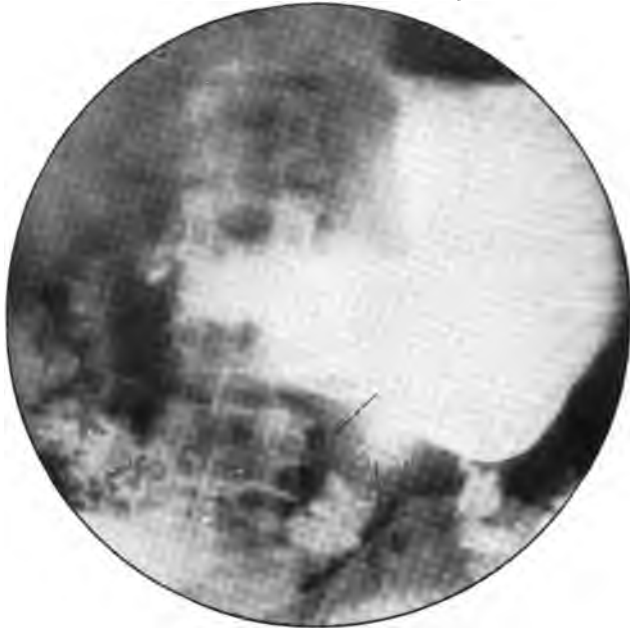


Fig. 60.—Case 69,645. Some irregularity of stoma at *a*, with narrowing of jejunum, *b*.

ulcer. Roentgenoscopy, February 5, 1914, showed the stomach quite large and mobile. Peristalsis was vigorous. There was no six-hour retention. The gastro-enterostomy was patent.

CASE 115,553.—First operation in 1906; anterior gastro-enterostomy for duodenal ulcer and hour-glass stomach. First roentgenoscopy September 21, 1914, showed retention of one-fourth the six-hour meal and a large hour-glass stomach. A niche appeared on the lesser curvature. There was hyperperistalsis. The

pylorus was very patent. The gastro-enterostomy was only moderately patent, with a slight irregularity about the stoma and narrowing of the efferent jejunum (Fig. 61).

A second operation was done September 26, 1914, for gastric and gastrojejunal ulcer, with excision of the gastrojejunal ulcer; posterior gastro-enterostomy.

A second roentgenoscopy, March 11, 1915, showed retention of

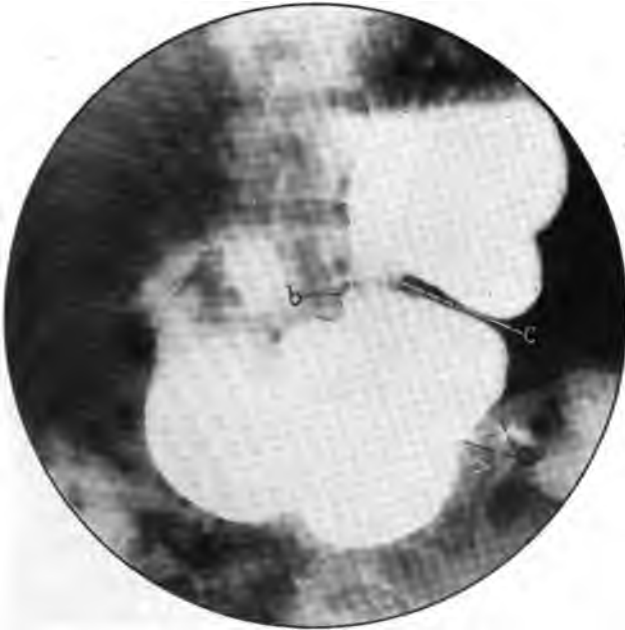


Fig. 61.—Case 115,553. (Prior to second operation.) Slight irregularity of stoma, *a*, which is not freely patent; niche of gastric ulcer on lesser curvature at *b*; hour-glass constriction at *c*.

half the six-hour meal, the residue being between the stoma and the pylorus. Notwithstanding this retention, after filling the stomach the gastro-enterostomy seemed patent. Some irregularity was noted about the stoma. There was an hour-glass stomach. Hyper-peristalsis and a niche on lesser curvature were observed (Fig. 62). A third operation was done March 18, 1915, for gastrojejunal ulcer.

CASE 83,614.—First operation May 14, 1913; anterior gastro-enterostomy for perforating duodenal ulcer. Roentgenoscopy,

October 13, 1914, showed the gastro-enterostomy functioning and marked spasticity of the stomach.

CASE 98,939.—First operation February 10, 1914; posterior gastro-enterostomy for obstructing duodenal ulcer. Roentgenoscopy, January 16, 1914, showed no retention; a stomach of moderate size with diminished mobility, and a patent gastro-enterostomy. A marked filling defect was noted on greater curvature about the stoma; also an irregularity of the first inch of the jejunum (Fig. 63).



Fig. 62.—Case 115,553. (Prior to third operation.) Some irregularity of stoma and jejunum at *a*; niche of gastric ulcer on lesser curvature at *b*; hour-glass constriction at *c*.

CASE 50,276.—First operation elsewhere in November, 1911; posterior gastro-enterostomy for duodenal ulcer. Roentgenoscopy, February 5, 1915, showed a large stomach with retention of one-fourth of the meal after six hours. Peristalsis was active; gastro-enterostomy not freely patent; pylorus free. The plates show some irregularity about the stoma. The duodenum was dilated, the jejunum narrowed.

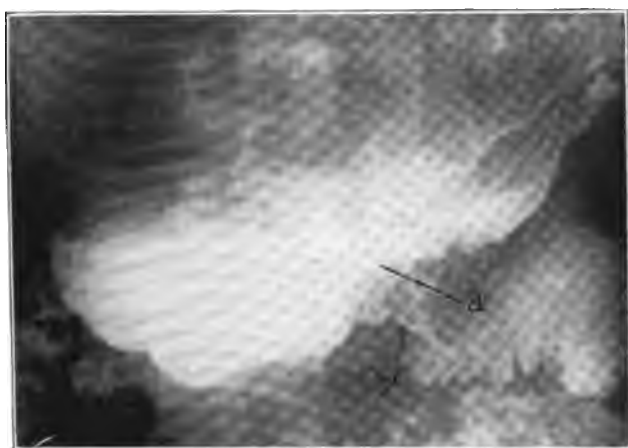


Fig. 63.—Case 98,939. Deformity about stoma at *a* and first inch of jejunum at *b*.

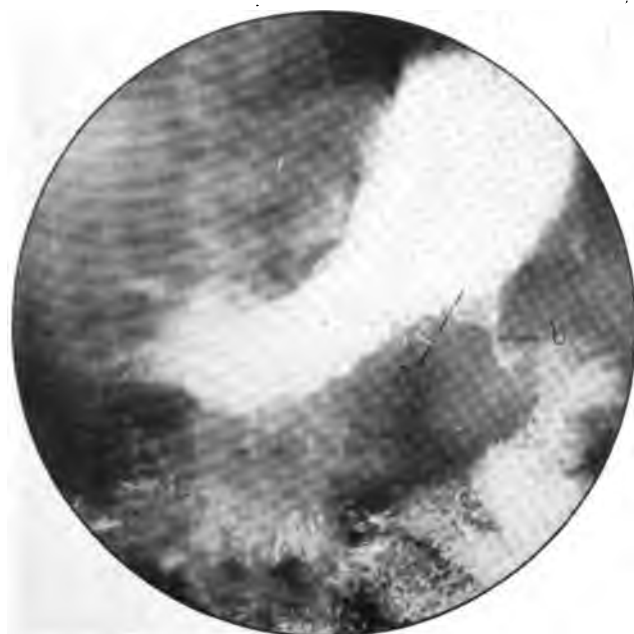


Fig. 64.—Case 101,024. Slight irregularity about stoma at *a*; narrowing of first inch of efferent jejunum, *b*.

CASE 101,624.—First operation March 9, 1914; posterior gastro-enterostomy for chronic perforating duodenal ulcer. Roentgenoscopy, April 27, 1915, showed no retention, the gastro-enterostomy very high on the stomach, and functioning moderately. The pylorus was quite free, the stomach of medium size and mobile, with active peristalsis. There was a slight irregularity of the greater curvature about the stoma. The jejunum was narrowed (Fig. 64).

CASE 96,667.—First operation December 12, 1913; posterior gastro-enterostomy for perforating duodenal ulcer. Roent-

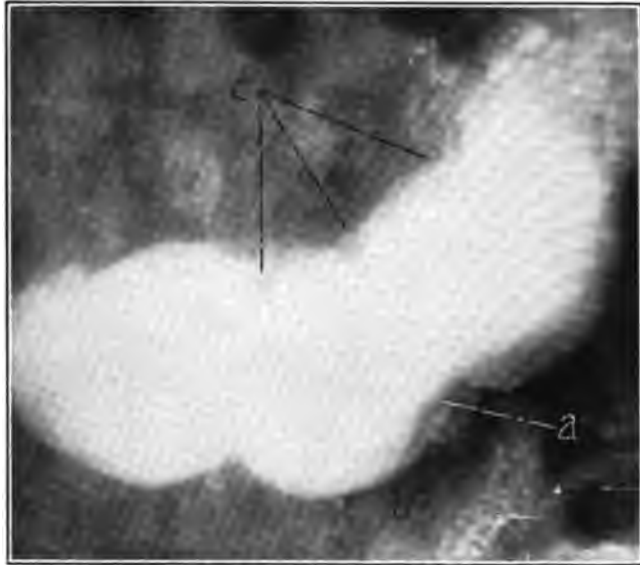


Fig. 65.—Case 96,667. Large stomach with deformity of stoma at *a*; narrowing of jejunum at *b*; note hyperperistalsis; peristaltic waves at *c*.

genoscopy, December 6, 1913, showed retention of half the six-hour meal. There was hyperperistalsis. The gastro-enterostomy was not freely patent; the stoma was irregular, the jejunum narrowed, the stomach large, the duodenal bulb irregular. The pylorus was free (Fig. 65).

CASE 131,378.—First operation, elsewhere, February 6, 1915; posterior gastro-enterostomy for reasons not known. Roent-

TABLE II.—FIRST AND SECOND OPERATIONS

CASE NUMBER	AGE	DATE FIRST OPERATION	FIRST OPERATION	FINDINGS FIRST OPERATION	DATE SECOND OPERATION	FINDINGS SECOND OPERATION	PROBABLE CAUSE OF GASTROJEJUNAL ULCER	SECOND OPERATION
12,869	64	Aug. 1, '08	Posterior gastro-enterostomy	Large perforating duodenal ulcer	June 12, '13	Large gastrojejunal ulcer, mostly gastric	?	Separation of gastro-enterostomy; modified Finney
60,645	55	Oct. 10, '12	Posterior gastro-enterostomy	Calloused duodenal ulcer	June 24, '13	Gastrojejunal ulcer	Knot of linen in region of ulcer	Excision of ulcer; gastro-enterostomy enlarged
76,684	46	Dec. 5, '12	Posterior gastro-enterostomy	Perforation gastro-enterostomy	Oct. 18, '13	Gastrojejunal ulcer, anterior margin	Linens hanging in anastomosis?	Excision of ulcer; gastro-enterostomy enlarged
101,545	46	1898	Anterior gastro-enterostomy; Murphy button	Pyloric obstruction	Mar. 17, '14	Large gastrojejunal ulcer	?	Anterior gastro-enterostomy
81,306	49	Mar. 24, '13	Posterior gastro-enterostomy	Large posterior duodenal ulcer; contact ulcer	Mar. 17, '14	Gastrojejunal ulcer	Linens hanging in anastomosis	Pylorus division gastro-enterostomy, enlarged
96,667	51	Dec. 12, '13	Posterior gastro-enterostomy	Large perforating duodenal ulcer	Oct. 12, '14	Gastrojejunal ulcer	Linens hanging in anastomosis	Finney on jejunum
83,614	48	May 14, '13	Anterior gastro-enterostomy	Large perforating duodenal ulcer	Oct. 19, '14	Gastrojejunal ulcer, indurated	?	Gastro-enterostomy cut off.
98,939	30	Feb. 10, '14	Posterior gastro-enterostomy	Obstructing duodenal ulcer	Jan. 27, '15	Jejunal ulcer, perforating posterior	? Interrupted silk suture	Resection pylorus Billroth No. 1
50,276	35	Nov., 1911	Posterior gastro-enterostomy elsewhere	Duodenal ulcer	Feb. 11, '15	Small gastrojejunal ulcer, abscess posterior	?	Finney on duodenum; gastro-enterostomy cut off; Finney pyloroplasty
101,624	40	Mar. 9, '14	Posterior gastro-enterostomy	Chronic perforation duodenal ulcer?	Apr. 30, '15	Large gastrojejunal ulcer	?	Gastro-enterostomy cut off
131,378	42	Feb. 6, '15	Posterior gastro-enterostomy elsewhere		June 2, '15	No evidence of gastric or duodenal ulcer; gastro-enterostomy high on fundus; gastrojejunal ulcer	Long loops silk sutures	Excision of ulcer; horse-shoe plastic
51,115	51	Apr. 1, '11	Posterior gastro-enterostomy	Large contracting duodenal ulcer	Feb. 29, '12	Large gastrojejunal ulcer, mostly gastric	?	Excised gastrojejunal ulcer; closure gastro-enterostomy
115,553*	44	June 29, '06	Anterior gastro-enterostomy	Duodenal ulcer; hour-glass stomach	Third operation Mar. 18, '15	Third operation, large gastrojejunal ulcer, contracted opening	Third operation, linen sutures in ulcer	Gastro-enterostomy cut off; Finney for stricture of healed duodenal ulcer
			Second operation, posterior gastro-enterostomy; plastic for gastrojejunal ulcer					Third operation; gastro-enterostomy cut off, Finney

* Second operation September 26, 1914.

genoscopy, May 24, 1915, showed a small gastro-enterostomized stomach with gastro-enterostomy functioning. There was no six-hour retention.

As will be noted, all the cases examined by the roentgen ray were of the non-fistulous type, yet all but two showed distinct roentgenologic signs of secondary pathology. These manifestations included deformity about the stoma, narrowing and deformity of the jejunum, diminished patency of the stoma, dilatation of the stomach, retention from the six-hour meal, hyperperistalsis, dilatation of the duodenum, and spasticity of the stomach. All these roentgenologic phenomena are in consonance with the pathology of the condition as found at operation. Recapitulating, we note:

Deformity of contour about stoma.....	8 cases
Exaggerated peristalsis.....	6 cases
Large stomach.....	5 cases
Gastro-enterostomy not freely patent.....	5 cases
Retention from six-hour meal.....	3 cases
Lessened mobility of stomach.....	2 cases
Irregularity of jejunal contour near stoma.....	5 cases
Dilatation of duodenum.....	1 case
Spasticity of stomach.....	1 case

The elicitation of these signs is favored by certain technical minutiae, the details of which may be of service to others engaged in this work. As to the opaque salt, whether barium or bismuth, the vehicle, whether fermented milk, corn-starch-pap, etc., the proportions of the mixture, and the total quantity given, each examiner has his preference. These matters are of importance only as affecting the functional behavior of the stomach, and it is merely necessary that comparisons be made always upon that basis with which the examiner is familiar. One part of the routine which we insist upon for our own examinations is the employment of a six-hour meal⁹ as a test of gastric motility. This meal consists of four ounces of cooked breakfast cereal mixed with two ounces of barium sulphate, and a little sugar and milk is permitted to be added if desired. It is given on a fasting stomach, and the patient is required to abstain from food until the examination, six hours later. During the screen examination, two ounces of barium sulphate in

eight ounces of water is given, followed by about three ounces of barium sulphate in twelve ounces of corn-starch-pap.

In every examination of the digestive tract, both roentgenoscopy and roentgenography should be employed. They should not be regarded as independent competitive methods, but as complementary parts of one method, for exclusive reliance upon either alone is likely to result in overlooking some important feature of a case. Roentgenoscopy is particularly necessary in examinations for gastrojejunal ulcer.

Deformity about the stoma in cases of posterior gastro-enterostomy is often not readily visible. If the point of anastomosis is well up on the vertical position of the stomach, an oblique view may show it, but it is much more commonly on the horizontal portion of the stomach. Here an oblique view is of little service, and we have often found it advantageous to lift up the overhanging lower border of the stomach by palpation and thus expose the anastomosis. While the point of attachment normally shows a little dimpling of the greater curvature, it is not markedly irregular. On the other hand, in many cases of gastrojejunal ulcer we have noted rather striking deformity about the stoma. In cases of high anterior or posterior gastro-enterostomy the lateral view may be of value. Gastrojejunal ulcer following an anterior gastro-enterostomy frequently produces a palpable mass which corresponds to the visible irregularity and filling defect about the stoma. This finding is almost pathognomonic. Since the gastro-enterostomy is often in the median line, pressure against the spine may deform this region and the examiner should be careful in his interpretation of plate findings. In making plates with the patient standing, he should be cautioned not to press the abdomen too tightly against the cassette. In the prone position his chest and hips should be supported by cushions, or a table with a deep fenestrum for the plate should be used. However, if the distortion about the stoma is sufficiently marked and identical on all plates, the observer may feel safe in saying that is abnormal.

Narrowing and deformity of the jejunum was observed in nearly half the cases of gastrojejunal ulcer. It involved the efferent limb

near the stoma (Fig. 64). This, also, should be definite and constant at the screen inspection and on all plates.

The signs of diminished patency of the stoma are both direct and indirect. Directly, the examiner can note the lessened amount of barium passing out, in contrast to the normal copious exit. If the flow is scant or wanting in spite of manual pressure of the gastric contents toward the stoma, it is reasonably certain that the opening is not free. While this finding is strongly indicative of



Fig. 66.—Stomach of average size. Small six-hour residue about stoma. Marked deformity of stoma and efferent jejunum, A. Pocketing of jejunum at B. Stomach not freely mobile. Peristalsis normal. Pylorus moderately patent.

gastrojejunal ulcer, it is not absolutely so, since I have recently noted a case in which narrowing was found at operation but without any evidence of ulcer. However, in this instance there was no deformity of the stoma itself, a sign which is really necessary for diagnosis. Indirectly, obstruction may be manifested by a retention from the six-hour meal, or by the large size of the stomach. Hyperperistalsis or dilatation of the duodenum and afferent limb of the jejunum may also be in evidence. Of these signs, the six-hour retention is most important. Occurring in a gastro-enterostomized

stomach, it is highly significant of obstructed drainage. In most of the cases of retention in association with gastrojejunal ulcer, the residue was between the stoma and pylorus. In one case the barium rest was in the immediate neighborhood of the stoma, as though held in a small pouch. This proved to be a gross ulcer with a pocket of considerable size in the jejunum, being exaggerated by adhesions. The usual gastro-enterostomized stomach, even though large before operation, tends to contract to normal or even smaller



Fig. 67.—Rather small stomach. Filling defect pars media, greater curvature about stoma at A. Irregularity and pocketing of jejunum, due mostly to adhesions, at B. No six-hour retention.

dimensions. If, then, it does not show diminution in size, but is still large, interference with its emptying may be suspected. Another common sequence of obstruction is an exaggeration of peristalsis. An increase in the vigor and number of the waves may also result from other causes, so that this sign is merely indicative of some abnormal condition. Dilatation of the duodenum was observed in one of our eleven cases, and this may or may not have been due to obstruction in the vicinity of the stoma.

Lessened mobility of the stomach was noted in two instances,

and was the result of extensive adhesions about the stoma. But this is a sign of which the observer can rarely be certain, especially when dealing with a posterior gastro-enterostomy. By palpation, changing the position of the patient, and requiring him to breathe deeply, fixation at the point of anastomosis can sometimes be fairly determined.

Spasticity of the stomach, as seen in one case, cannot be con-

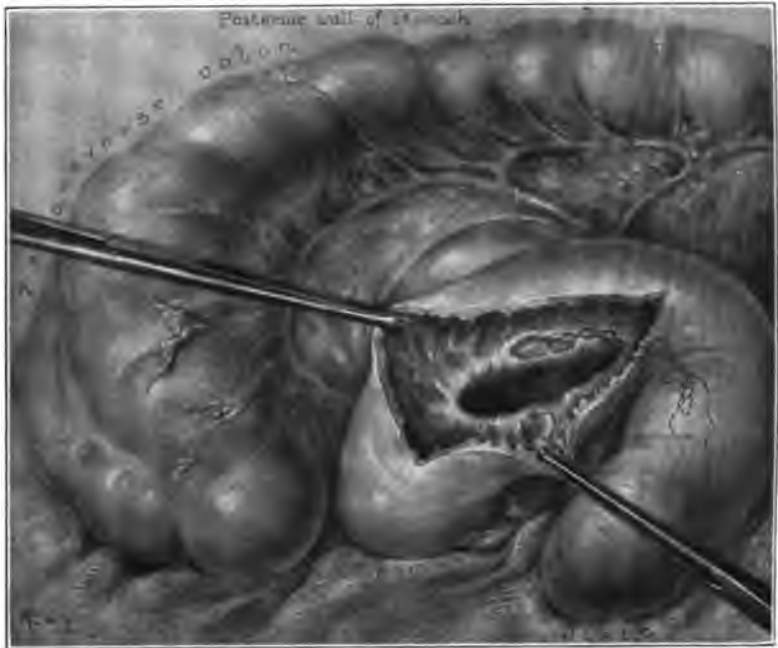


Fig. 63.—Stitch attached in gastrojejunal ulcer with end hanging in jejunum. Note the scar tissue behind the ulcer causing permanent thickness and adhesions.

sidered very significant except as a minor indication of reflex irritation.

In translating the observation of these signs into a diagnostic opinion the examiner should be fully acquainted with the entire history of the case, the nature of the primary lesion, and the character and extent of surgical intervention. The roentgen phenomena fall into two groups: those broadly denoting an abnormal condi-

tion, and those pointing directly to the seat of trouble. Six-hour retention, hyperperistalsis, large size of the stomach, dilatation of the duodenum, and spasticity of the stomach are included in the first group. They may be noted singly or in varying combinations. The second group, namely, deformity about the stoma, narrowing of the jejunum, scant flow of barium through the gastro-enterostomy opening, and fixation of the stomach at the site of anastomosis, all point to the latter as the pathologic focus, and here gastrojejunal ulcer is by far the commoner active lesion. In a stom-

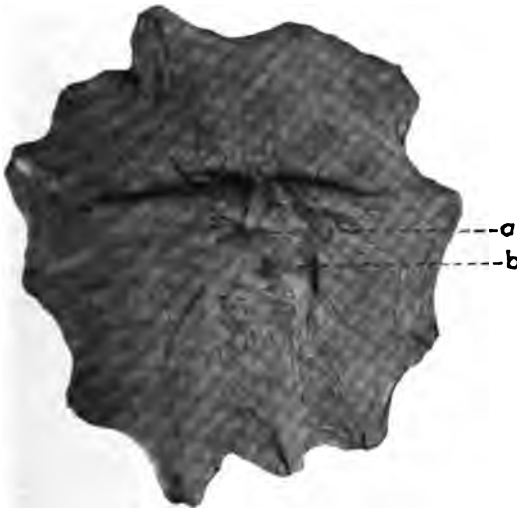


Fig. 69.—Small ulcer, about 1 cm. in diameter, around the suture; *a* locates the puckering of the healed mucosa; *b* is the ulcer, near the center of which is the suture.

ach resected for cancer, similar signs might result from a recurrence of the growth at the point of gastro-enterostomy. The history should make distinction easy.

The gross pathologic picture in our own cases and in those reported in the literature is more or less constant. The ulcers we have observed were of considerable size, from 1 to 3 cm. in diameter. They actually involved the anastomosis, with a tendency to spread to greater extent on the jejunal than on the gastric side. Common to all and most striking is an associated marked indura-

tion of the entire line of anastomosis with firm adhesions to surrounding structures. This in three of the cases produced a palpable mass, especially prominent in the anterior gastro-enterostomy cases. Subacute perforation has been the rule, and in one case produced a fistula between the stomach and transverse colon.

Of greatest interest in the findings has been the discovery of strands of unabsorbed permanent suture material in 6 of the 13 cases (Figs. 68 and 69). This retained suture material must have constituted an important etiologic factor. The condition has been reported by other observers. So far as can be determined, Berg¹⁹ reported the first case of retained suture material following gastro-enterostomy. The patient had had an anterior gastrojejunostomy in 1895 for pyloric stenosis. In 1898 Berg reoperated by the Roux method, and the tissue removed showed a gastrojejunal ulcer in which was a coil of retained silk suture.

Regardless of whatever associated conditions may exist which predispose to the formation of these ulcers, we must accept the retained unabsorbable suture as of immediate importance. In the Mayo Clinic as a means of prevention the technic for gastro-enterostomy has been modified to the extent that—(1) A few interrupted sutures of fine silk are used as stay-sutures for the serosa, and (2) running sutures of chromic catgut are used for all other purposes. Strangulation of tissue by sutures is avoided in these cases, the mucosa is carefully coaptated, accurate hemostasis is sought, trauma avoided, and a sufficiently large opening, suitably placed, is made.

There is no one surgical procedure which can be adopted as an operative measure in the treatment of all gastrojejunal ulcers. The difficulties which the individual case presents are usually dependent on marked induration and inflammatory changes surrounding the anastomosis. In the presence of this induration and infection plastic operations on the anastomosis with removal of the ulcer are associated with corresponding technical difficulties. Nevertheless, this is the general indication and proves itself to be the method of choice in the majority of cases. In some it has been possible and advisable to excise the anastomosis, close the openings in the stom-

ach and jejunum, and do a pyloroplasty, an operation, however, which also prevents difficulties on account of the scar tissue which always exists in the neighborhood of the original ulcer.

Transgastric excision may be satisfactory in an occasional case, Moynihan reporting a good result from this method in one instance.

The general plan, therefore, in the light of our present information, is to expose the line of anastomosis by either a transgastric or transjejunal incision, search for retained suture and for the ulcer, remove both, the latter either by itself or with the entire anastomosis. If the anastomosis is constricted and enlargement possible and safe, such treatment is satisfactory; if, however, much induration and infection exist, excision of the anastomosis, closure of openings, and gastroduodenostomy are indicated.

It is to be expected that an operation which has developed such wide-spread and warranted popularity as gastro-enterostomy should occasionally be associated with results which are not satisfactory; yet the comparatively low percentage of patients who are not relieved of their symptoms by gastro-enterostomy should not deter us from investigating the causes of these few failures and attempting still further improvement in their diagnosis and prevention.

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THE ESSENTIAL FACTORS IN THE DIAGNOSIS OF CHRONIC GASTRIC AND DUODENAL ULCERS *

GEORGE B. EUSTERMAN

This review is undertaken to emphasize proved clinical factors and briefly to consider various phases of experimental, clinical, and therapeutic advancement in their application to the diagnosis of benign, chronic gastric and duodenal ulcers. Our observations are based on the study of 2400 cases of gastric and duodenal ulcers operatively demonstrated in the Mayo Clinic from 1900 to 1914, inclusive, with an especial summary of the cases of 1913 and 1914.

DIAGNOSIS

A skilful anamnesis, in the absence of extensive clinical observations or direct roentgenologic evidence of a lesion, is still the most important factor in the differential diagnosis of lesions causing gastric disturbance. With regard to ulcer, characteristic chronicity or remission of symptoms is readily apparent in the case records in over 80 per cent. of all our proved cases. The principles emphasized by Graham¹ since his earliest observations are as effective today as then, and are the accepted diagnostic criteria in a large daily experience. Pyloric and duodenal ulcers in which complications are not far advanced invariably manifest periodic exacerbations. Seasonal variations, especially of spring and fall, appear in almost 40 per cent. of all cases. Nervous and physical fatigue, infection and exposure, dietetic indiscretions, toxic intestinal disturbance, etc., are prominent factors influencing recurrences. Be-

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tween seizures complete relief from symptoms is the rule, although frequently in ulcers situated well up along the lesser curvature remission rather than periods of complete relief may occur. In general the greater number of these patients have had symptoms for from five to twenty years, in our experience, few less than one, and a constant average of twelve and one-half years. During the period of attack, pain or distress, variable in character and intensity, is the common and constant symptom in nearly all cases.

Of secondary diagnostic significance are the location, type, and area of radiation of the pain. The time of pain and method of its control are of primary importance. The complex of chronicity and periodicity of attacks in which pain or distress and the usual association of symptoms repeated uniformly day by day during the attack and bearing a fairly definite relation to food intake and control are of primary clinical importance in the diagnosis of 80 per cent. of cases of uncomplicated peptic ulcer. In the remaining 20 per cent. this complex may be irregular, atypical, or almost entirely absent; or the symptoms may be "mixed," owing to coincidence of disease in contiguous organs, which occurs in about 16 per cent. of all cases of ulcer. It is this group which often taxes the resources of the clinician, but errors in diagnosis do not easily occur if the possibilities are constantly borne in mind, especially: (1) In cases in which a perforative process or a painful spasm simulates hepatic colic; (2) in cases in which ulcers had become chronic and complicated when the first symptoms appeared; and (3) in cases suggesting a malignant process, the result of an extensive ulcer, hemorrhage, cachexia, and perhaps a palpable inflammatory mass.

Clinical differentiation between gastric and duodenal ulcer is extremely difficult and in most instances well-nigh impossible. This has been the opinion of most observers. With great regularity late pain and the nature of hemorrhage in proved gastric ulcer may suggest duodenal lesion. Then, too, not infrequently the earlier onset of pain in some cases of duodenal ulcer suggests gastric lesion. In about 5 per cent. of all ulcers coincident lesions in the stomach and duodenum are noted, an incidence which increases our difficulties. In our experience and in that of many

other observers the roentgen ray is of inestimable value. In this field it has its most practicable application, besides occasionally furnishing the first reliable evidence to indicate the presence of ulcer; but too great reliance must not be placed on this; for, valuable as may be the information afforded by the roentgen examination, it has its limitations. The degree of demonstrability of gastric ulcer is directly concerned with three factors: that is, position, size, and depth of the ulcer. The direct sign of irregularity of the gastric contour (niche, accessory pocket) may be wanting in instances in which the ulcer is situated on the anterior wall, high up in the cardia, and when it involves the pyloric segment; should it be shallow, "slit-like," it may not be successfully demonstrated.² Indirect and auxiliary signs, however, in combination with clinical data, may be helpful in establishing the diagnosis. The strikingly frequent occurrence of bulb deformity or hyperperistalsis with residue in duodenal ulcer is worthy of note from both the point of diagnosis and localization.

The continuous or intermittent presence of altered or fresh blood in the gastric extract, the absence of evidence pointing to gross motor disturbances, and the situation of pain and tender point to the left of the median line are strong presumptive evidence of gastric ulcer. Clinically, this general observation can be made: Uncomplicated types of duodenal and pyloric ulcer are invariably clear-cut throughout their life history; the longer the period between intake and pain, the lower the ulcer, as a rule; the more prompt the onset and the briefer the duration of pain, the higher the ulcer. In ulcer of the stomach proper this may not be so clear-cut as in duodenal or pyloric types, nor are the day-by-day symptoms so clearly defined. In ulcers well above the pylorus the symptoms are likely to be continuous, or remissions rather than intervals of complete relief are likely to be noted. The pain is not so often relieved by food; small amounts of food may give relief, while increased amounts may cause distress; more care as to diet is necessary; if bleeding occurs, hematemesis predominates; vomiting plays a more frequent rôle, even in the absence of obstruction, and affords relief; soda relieves pain when food does not; pain

begins earlier, as a rule, often disappearing before the next meal, for obvious reasons, in the absence of stasis or marked hypersecretion. Thus the food-relief is minimized; but pain from one-half hour to two hours after food is quite the rule and is of diagnostic significance. Too much clinical significance cannot be placed on reliable evidence of gross hemorrhage in the presence of other symptoms characteristic of ulcer. This complication, however, occurs in only about 35 per cent. of all chronic gastric and duodenal ulcers. The association of hemorrhage with the ulcer-complex makes for safe diagnosis of ulcer in 95 per cent. of all cases. In 5 per cent. of all ulcers there is a silent bleeding type in which blood is regularly found in the stools, but more or less complete absence of other usual clinical symptoms of pain, hyperacidity, and food ease. Benign ulcer, unlike cancer, bleeds intermittently. Positive analysis of occult blood in the stool on limited examination was present in about 25 per cent. only of the cases studied. Hemorrhage has been noted in 2 per cent. of all cases of chronic appendicitis associated with marked gastric disturbance, while it is as high as 5 per cent. in chronic cholecystitis associated with the gastric reflex. In these cases the hemorrhage is probably due to primary follicular ulceration of the gastric or duodenal mucous membrane. More extensive observations on the frequency of occult blood, of general blood morphology and its diagnostic significance in ulcer, are now under way and will be the subject of future consideration.

Briefly stated, in those organic conditions which most frequently cloud the diagnosis—chronic cholecystitis and cholelithiasis, chronic appendicitis, etc.—we obtain our greatest diagnostic aid from the irregularity of symptoms during the period of attack. This irregularity is chiefly concerned with the time of appearance of pain and the influence of food. Nothing follows in sequence day by day, perhaps due to the fact that the stomach behaves properly unless irritated by the contiguous lesion, and this extrinsic lesion is irregular in its influence. Judging from our case-records, chronic catarrhal or “strawberry” cholecystitis very perfectly and most frequently simulates the ulcer-complex. The features of chronicity and “spells” (of invariably briefer duration, however) with

characteristic pain, hyperacidity, and flatulency having some food relation, the absence of colic, icterus and localizing signs are not uncommon. In order to lessen diagnostic error, daily clinical observation, repeated gastric analyses under variable circumstances, examination of the feces and, finally, the therapeutic management based on the well-known principles laid down by Sippy³ may be necessary. It is unnecessary to comment on the importance of having in mind and recognizing these types of chronic painful dyspepsia most frequently having their origin in these extragastric lesions. Of considerable moment, too, is the frequency of lesions coexistent in the gastroduodenal, biliary, pancreatic, or appendiceal systems, in which disturbances engendered by one may overshadow or make irregular the symptomatology of the other so that to the conceits of surgery must be left too frequently the ultimate diagnosis.

Test-meal analysis so essential to gastric diagnosis has also its limitations. In the absence of definite evidence of blood stasis, hypersecretion in the fasting contents, cardiac obstruction, etc., the findings are of value in so far as they are correlated with the clinical and roentgenologic data. They constitute a link, often a decisive one, in the chain of evidence. The instances of normal or subnormal acid value in the presence of a peptic ulcer occur in about 20 per cent. of all cases; on the other hand, hyperacidity and hypersecretion, even stasis of the first degree, are only too frequently associated with functional states, ptosis, and extragastric lesions. These conditions would soon lead to diagnostic confusion if too much dependence were placed on a single or even a repeated gastric analysis. Again, on account of purely physical conditions a considerable residue may be overlooked as shown by the contribution of Harmer and Dodd.⁴ This disadvantage can be largely overcome by the use of a lavage tube of proper consistence, calibration and ample fenestration, such as is now in common use. The researches of Rehfuess⁵ and his associates have made us revise our estimate of the normal contents of the fasting stomach. In selected cases the fractional study of gastric digestion by means of Rehfuess' tube and methods has proved to be of practical diag-

nostic value. Hyperacidity is the rule in 60 per cent. of cases of gastric ulcer and hypersecretion, also in ulcers at or near the pylorus. These features, singly or combined, are noted in 75 per cent. of all duodenal ulcers. A considerable hypersecretion of 200 c.c. or more, likewise the recovery of retention contents of our modified Riegel meal after from twelve to fourteen hours, invariably argues for a lesion or organic stenosis, especially if the findings are constant. The determination of gastric motility is of diagnostic importance second only to secretory function or disturbance and for obvious reasons the former is of especial interest to roentgenologists.

Carman and Miller⁶ conclude that their bariumized carbohydrate-meal method is a more sensitive test for gastric motility than the modified Riegel meal as commonly used in our clinic; that the modified Haudek double-meal method is more informative than tubing after a motor-meal test, since the former not only shows delay of evacuation beyond six hours, but also yields information as to hypermotile conditions. Their conclusions are based on a comparison of results of both examinations in 950 patients who came to operation. The lesions were as follows: appendix, 125; gall-bladder, 311; gastric ulcer, 109; gastric cancer, 137; duodenal ulcer, 268. Of these patients, 220 (23.1 per cent.) showed a six-hour barium residue; 131 (13.7 per cent.) had food remnants after fourteen hours or longer. The majority (209, or 90.4 per cent.) of the 220 patients showing a barium retention were found to have cancer or gastric or duodenal ulcer. They further conclude that a distinct residue after six hours from the barium meal given under prescribed conditions was in 90 per cent. of instances indicative of grave pathology, and usually denoted obstruction at or near the pylorus.

From personal observation we may concede a more sensitive test for motility in this method, especially in case of intermittent or low-grade retention dependent on pylorospasm, incomplete stenosis, and on lesions of the accessory digestive system. One may add that the comparison of results between the two methods is hardly fair, principally because of difference in the time element

and other features which must be taken into consideration. The motor meal, under proper circumstances, will continue to be a most practicable index of gastric motility—a fact conceded by eminent roentgenologists and emphasized by clinicians following observations made from the results of both methods. By the latter method one has the additional advantage of being able at the same time to estimate the secretory function of the stomach.

STATISTICAL STUDY

Exclusive of those cases in which a consistent diagnosis of gastric or duodenal ulcer was made and medically treated, there were 1078 cases operatively demonstrated during the years 1913 and 1914. Of these, 264 were gastric and 814 were duodenal. Coexistent lesions in both organs were noted in 44 (4 per cent.). The average ratio of gastric to duodenal ulcers is well shown in this series, about 1 to 3, that is, 75 per cent. of the ulcers were duodenal. Of the 264 cases of gastric ulcer, 171 occurred in males and 93 in females. The average ages were 47 and 44.5 years, respectively. The average duration of symptoms was 9.8 years. In about 80 per cent. the course was intermittent, free intervals alternating with "spells" of variable duration, regular (40 per cent.) or irregular (49.5 per cent.) in frequency. In 50 per cent. the complaint was continuous and progressive over periods of from several months to several years prior to operation. Irrespective of the situation of the ulcer, pain appeared within four hours after meals in 85 per cent. of the cases; in over 30 per cent. it was present within two hours; in 55 per cent. within three hours, regarded as constant in 3.8 per cent. and irregular in 3.4 per cent. Definite nocturnal pain occurred in only 6 cases, or 2 per cent. Pain was controlled by food or alkalis, or both, in 180 cases. The majority of these (84 per cent.) showed relief after food, while alkalis alone gave relief in 15.6 per cent. There was a fairly definite history of bleeding (hematemesis or melena) in 73 cases, or 27.6 per cent., of this group; about 41 per cent. had hematemesis only, 15 per cent. melena, while both hematemesis and melena were mentioned in 44 per cent.

Gastric analyses were carried out in 255 cases; 38 per cent. of

these showed presence of altered blood in the extract. Gross retention was evident in 33.3 per cent. The average total acidity was 54; the average hydrochloric acid was 42. In 18 per cent. the acid values were normal or below normal. The absence of free hydrochloric acid was shown in 13 cases. Under such a circumstance the possibility of carcinoma, syphilis or associated disease was evident. Five of these patients have since died from malignancy, three now apparently show malignancy; in the others the advanced age associated with considerable fresh blood in the extract, gall-bladder disease, or other pathologic lesions explained the achlorhydria.

The generally accepted complex of ulcer was more or less definitely present in 81 per cent. of the 212 cases; irregular but suggestive in 6.8 per cent.; classified as irregular in 5.3 per cent. In the remaining 7 per cent. the picture was atypical or the record was incomplete. A primary diagnosis of gastric ulcer was made in 174 cases (66 per cent.); an alternative one in 21 cases (8 per cent.). Duodenal ulcer was the primary diagnosis in 47 cases (27 per cent.). The roentgen ray gave definite assistance in 65 per cent. of the 113 cases examined in this series.

The situation of the ulcers was as follows: the lesser curvature in 167 cases (63 per cent.); the pylorus, 35 (13 per cent.); total ulcers at or near the pylorus, 87 (33 per cent.); posterior wall, 27 (10 per cent.); anterior wall, 6 (2 per cent.); 2 gastrojejunal ulcers secondary to gastro-enterostomy. Multiple ulcers were noted in 15 cases (5.6 per cent.).

The complications were: advanced cicatricial pyloric stenosis, 11.7 per cent.; evidence of perforation, 28 per cent.; perigastritis with adhesions to neighboring structures, 28 per cent.; questionable malignancy, 11.7 per cent.; appendiceal disease, 33.7 per cent. In less than 25 per cent. of all cases there was no complicating factor, a fact which illustrates the advanced stage of the process at the time of first examination.

Of 814 cases of duodenal ulcers 628 (77 per cent.) were males and 186 (22.8 per cent.) were females. This characteristic disproportion in sex incidence Wilkie⁷ has probably explained on an anatomic basis. The average age was forty-three years and the aver-

age duration of symptoms was over twelve years. The clinical course was intermittent in 95 per cent. of all cases, and periodic in 50 per cent. Continuous preoperative complaint of variable duration was noted in 26 per cent. In more than 85 per cent. the pain appeared in from two to five hours after taking food; in the remainder it appeared within two hours. Nocturnal pain only was given in 6 cases (7 per cent.). Definite relief by food was noted in 67 and partial or irregular relief in an additional 15 per cent. Relief by neutralization was present in 39 per cent. Hemorrhage was reported in 208 cases (25 per cent.) and was classified: melena, 8.8 per cent.; hematemesis, 6 per cent.; both melena and hematemesis, 10.5 per cent. The acid values averaged 20 per cent. higher than in gastric ulcer and in only 7 per cent. were they below the accepted normal standard.

A primary clinical diagnosis was made in 543 cases (66.7 per cent.) and an alternative one in 67 cases; that of primary gastric ulcer in 88 cases (10.8 per cent.). This totaled 85.7 per cent., the usual average in the series recently studied. Of 251 cases in which the tentative diagnosis of gall-bladder disease was also made, 51 (20 per cent.) showed this disease present and 51 ulcers (22.3 per cent.) were shown to be chronic perforating. Reviewing the case histories, the ulcer complex was fairly regular in 71 per cent., suggestive in 7.2 per cent., and irregular in 13.2 per cent.

At operation advanced pyloric stenosis was shown in 251 cases (30.8 per cent.); perforation in 26.8 per cent.; periduodenal inflammatory disease in 23.5 per cent. Associated disease in the appendix occurred in 40 per cent.; in the gall-bladder in 9.7 per cent.

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DIAGNOSIS OF CHRONIC GASTRIC AND DUODENAL ULCERS 183

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NOTES ON GASTRIC AND DUODENAL ULCERS*

CHRISTOPHER GRAHAM

The questions often arise: Are there any symptoms or a group of symptoms whereby we may reasonably locate peptic ulcer? Do clinical histories, as ordinarily taken, give satisfactory evidence as to whether the ulcer be high or low? When the full evidence is before us, we often feel that the picture is reassuring, and when reviewing histories taken by other clinicians, we find symptoms repeated so frequently that we have hopeful moments. However, after reviewing the histories of our own cases from 1906 to 1915 we cannot find any pathognomonic symptom, or combination of symptoms, that clearly gives the coveted assurance, and we are forced to conclude that he who meets defeat again and again, in attempts at ulcer location, will, in time, even when the symptoms have met most of his requirements, come to feel less sure in his diagnosis than is comforting.

The clinical diagnoses in our series of approximately 1300 cases of operatively demonstrated duodenal ulcer during the years mentioned above have run about as follows: There were 702 (54 per cent.) cases primarily called duodenal ulcer, while 323 (24.8 per cent.) were classified as gastric ulcer. In another group of 107 (8.2 per cent., repeated) gastric or duodenal ulcer was given as the secondary diagnosis, or was considered equally with the lesion in question as the cause of the complaint. One hundred seventy-five cases (13.5 per cent.) were primarily considered gall-stones (5 per cent. gall-stones alone), or gall-stones entered largely into the diagnosis (8.5 per cent.).

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In 64 cases (5 per cent.) appendicitis (1 per cent. appendicitis alone) entered largely into the diagnosis, while cancer was considered in $1\frac{1}{2}$ per cent. About 1 per cent. were quite unclassified.

Among the 450 cases of gastric ulcer operatively demonstrated, 248 (55 per cent.) were classified as gastric, 119 ($26\frac{1}{2}$ per cent.) as duodenal, and 31 ($6\frac{1}{2}$ per cent., 19 gastric and 12 duodenal) in which the gastric diagnosis was placed second. The gall-bladder was primarily considered diseased in 40 (8.8 per cent.) cases, and in 5 per cent. this was the only diagnosis made. Cancer was considered present in 4.8 per cent. of the cases, appendicitis in 1.7 per cent., those not classified about $2\frac{1}{2}$ per cent. From these figures it will readily be seen why one hesitates in many cases to attempt to make a possible diagnosis as to the location of the ulcer. It is not a difficult problem to diagnose the presence of a peptic lesion, but it is quite difficult to determine whether the lesion is gastric or duodenal.

We have fallen into the way of roughly dividing gastric complaints into those of regular and of irregular types, and also of considering a gall-bladder type. However, one must keep in mind extrinsic causes, such as gall-stones, appendicitis, and tuberculosis. These may give quite the regular gastric syndrome, and gastric symptoms be the chief complaint for which relief is sought, or they may very often give an irregular history, which confuses and leads to provisional diagnoses.

The following clinical syndromes are worthy of consideration:

1. *The regular type of duodenal ulcer* is looked upon as that in which the pain or distress comes within two to five hours after meals, accompanied by gas, sour stomach, and vomiting, one or all appearing about the same hour, and continuing until the next meal, or until food, an alkali, vomiting, or irrigation brings comfort by relieving the acid state. These symptoms are repeated with certain uniformity each day for days, weeks, or months, and then there is an intermission of perfect ease, or at least a marked remission ensues. These periods of attack and intermission may come and go for years, the only change, perhaps, being an increase in

severity until the time comes when complications have altered the gastric movements and functions.

2. *The regular gastric type*, as we prefer to consider it, has the same periodicity and the same group of symptoms, though not so clearly cut as in the duodenal lesion, but, as we have shown, in at least one-fourth of the cases the difference is quite indistinguishable. Pain or distress comes sooner after meals, does not continue so clearly to the next meal, may cease for a time to begin again before the following meal, and is often eased by food, though not so often nor so clearly as the pain of duodenal ulcer. Fear of food-pain is more often noted. Food in small amounts gives ease, while in larger amounts it gives pain. Hunger-pain is not so clear cut, and not so frequent, because the pain may pass before mealtime arrives. Careful diet seems to give more relief than in duodenal ulcer, unless complications are present. Sour food is not so troublesome in the high as in the low ulcer, and the position of the body as well as physical activity plays a more important ease rôle in the gastric than in the duodenal cases. A definite intrinsic gastric complaint runs throughout the history, though the features seem less clear-cut than in duodenal ulcer, and one feels a greater lack of certainty in the diagnosis. However, the fact remains that the final diagnostic figures in this series hold clearly as well in the gastric as in the duodenal types.

3. *The irregular peptic ulcer type* of history has lost the distinctive *time of onset of symptoms* and their control. We find such histories in cases of obstruction, perforation with adhesions, hour-glass stomach, saddle ulcer, lesions of large areas, or any condition where function and movement are limited.

Intermissions or remissions are fairly constant, but not so well defined as in uncomplicated ulcer found low, or even usually those well above the pylorus. This type of history does not give that daily distinctive time of onset and control of symptoms which we expect to see during the period of an attack. They do not run that clear-cut course, yet when considered day by day, and week by week, we discover in the so-called irregularity a certain definite course which clearly points to an intrinsic lesion of the stomach.

Day by day the average is quite the same, though usually the hunger-pains, food-ease, and hemorrhages are less definite. However, pain, vomiting, distress, gas, and sour eructation are the constant results of food intake, from which more or less relief is experienced by careful diet, alkali, irrigation, or vomiting. These factors are always first in the patient's complaint, and are the ones most considered in the diagnosis. This irregular complicated type of history may be manifest from the first onset of symptoms, but often the early history, carefully developed, brings out the clear-cut typical history which supplies the final diagnostic point.

Histories in cases of high ulcer tend earlier to this irregular type, those of pyloric and duodenal ulcer less often, and then usually when obstruction or other complications have intervened. Thus, in the so-called irregular types we incline to the diagnosis of gastric rather than of duodenal ulcer, or we look for extrinsic causes. When gastric symptoms predominate, we must always bear in mind these extragastric causes whether they be general diseases or local conditions. At times the course of these extragastric lesions may be so typical of ulcer, even to the extent of hemorrhage, that ulcer is diagnosed unconditionally. Fortunately, however, the day-by-day symptoms in these cases vary so much—today this effect, tomorrow quite different, again a day entirely free, and through it all no change in diet or surroundings—that one catches the hint and guards the diagnosis. With patients complaining of gastric distress it is necessary to be constantly on guard, always ready to differentiate the extrinsic causes that simulate the regular ulcer type, as well as to differentiate those that seem to be of the irregular ulcer type, but are also as surely due to extrinsic causes. It is among the symptoms due to an extragastric condition that many difficult diagnostic battles are fought and lost, or but partly won, and it is these same difficult battles that have taught us to hesitate before making a too spirited diagnostic charge at the real enemy.

When reading duodenal histories one is apt to be impressed with the array of so-called regular histories, and to feel that ulcers higher up are not nearly so clear-cut. Yet in going over the histories from 1906 to 1915, we discovered that 72 per cent. of duodenal cases gave

fairly regular symptoms, and that 71 per cent. of gastric cases gave the expected syndrome, or were so clearly gastric that little hesitancy was felt in making a diagnosis.

Pain is the one constant diagnostic factor in all peptic ulcers. Less than 1 per cent. of patients are recorded free from pain. The character of the pain has few if any distinguishing points, and is described as: distress, aching, burning, gnawing, pressing, boring, sharp cramps, colic, etc. It runs a similar course in all ulcers, though it resembles the pain in gall-stone cases more frequently in the duodenal group. The time of pain has some distinctive diagnostic significance. In the duodenal ulcers the pain came one-half to two hours after food in 23 per cent. of cases, and two to five hours in 77 per cent. of the cases. In gastric ulcers the time limits of one-half to two hours included 50 per cent. and two to five hours an equal number. In 20 per cent. of the duodenal and in 19 per cent. of the gastric ulcers the time of pain was not recorded. Eight per cent. of the patients with duodenal ulcer, and 19 per cent. with gastric ulcer, had pain within one-half to one hour after eating.

Pain at night appeared to be more decidedly frequent in duodenal ulcer, while ease from posture (lying down) seemed decidedly more frequent in gastric ulcer. However, the final analysis gives 14 per cent. of the patients with duodenal ulcer and 10 per cent. of those with gastric ulcer having pain at night. Postural ease was noted in 8 per cent. of the duodenal and in 9 per cent. of the gastric cases. These figures correspond much more closely than one would suppose from impressions gained in history writing.

Continuous pain from the beginning of symptoms was mentioned in 4 per cent. of the duodenal and 9.5 per cent. of the gastric cases. Tenderness to touch was recorded in 41 per cent. of the duodenal and 40 per cent. of the gastric histories.

The location and radiation of pain were noted as follows: Of the duodenal ulcers, 49 per cent. were well confined to the epigastrium; 52 per cent. of the gastric were similarly located. Those with radiation to the back ran 24 per cent. duodenal and 22 per cent. gastric. In the diagnosis gall-stones were considered certain or

were given first place in 13 per cent. of the duodenal and in 9 per cent. of the gastric cases.

Radiation to the left epigastric area occurred twice as often in gastric (10 per cent.) as in duodenal cases (4 per cent.). The percentage of radiation to the abdomen and fossæ was quite similar (9.5 per cent. duodenal, 9 per cent. gastric). Radiation to right epigastrium was present in 6.6 per cent. of the gastric and in 13.7 per cent. of the duodenal cases. Therefore, tenderness to touch, radiation of pain, and the patient's ability to locate his subjective pain gave little basis upon which to arrive at a differentiation. The pain, as described by the patient, had much the same character in both the gastric and duodenal type—so much so that it gave but little clue to the location of the lesion. However, when ulcers were high there was some diagnostic foundation in the patient's ability to locate his subjective pain. In some instances the pain was quite to the left side, or even well under the left arch.

Vomiting was recorded as occurring in 79 per cent. of the duodenal and in 82 per cent. of the gastric ulcers, while gas was present in 77 per cent. of the duodenal and in 94 per cent. of the gastric. With the vomiting and gas, sour gastric contents were quite constant in both types, though more troublesome in the gastric.

Control of pain, whether the lesion was in the duodenum or above, ran quite the same and was as follows:

Food or drink, or both, eased pain in 75 per cent. of duodenal and in 66 per cent. of gastric ulcers. Vomiting and belching of gas had less distinguishing percentages, both giving marked ease. Ease from belching of gas in each was less permanent than vomiting. However, gas-formation and belching were more persistent in patients with ulcers of the pylorus.

The effect of alkalis was practically the same wherever the location, *i. e.*, ulcers above the pylorus were about as frequently (33 per cent.) eased as those in the duodenal area (38 per cent.). Irrigation gave about the same results no matter where the lesion (11 per cent. in duodenal and 9 per cent. in gastric), the advantage lying slightly in favor of the duodenal location.

Gastric hemorrhages may be of some diagnostic aid. In this

series, history of hemorrhages by the mouth was recorded in 18.5 per cent. of duodenal and in 25 per cent. of gastric cases. Blood by the bowels was similarly recorded in 18 per cent. of duodenal and in 24 per cent. of gastric cases.

COMPARISON OF CLINICAL DIAGNOSES IN CASES OF OPERATIVELY DEMONSTRATED DUODENAL AND GASTRIC ULCERS

1300 DUODENAL ULCERS	CASES	PER CENT.	451 GASTRIC ULCERS	CASES	PER CENT.
CLINICAL DIAGNOSIS					
Primary diagnosis, duodenal ulcer	702	54.0	Primary diagnosis, gastric ulcer	248	55.0
Primary diagnosis, gastric ulcer	323	24.8	Primary diagnosis, duodenal ulcer	119	26.5
Secondary diagnosis, duodenal or gastric ulcer (repeated)	107	8.2	Secondary diagnosis, gastric or duodenal ulcer (repeated)	31	6.5
Primary diagnosis, diseased gall-bladder (gall-bladder alone, 5 per cent.)	175	13.5	Primary diagnosis, diseased gall-bladder (gall-bladder alone, 5 per cent.)	40	8.8
Primary diagnosis, appendicitis (appendicitis alone 1 + per cent.)	64	5.0	Primary diagnosis, appendicitis	8	1.7
Primary diagnosis, cancer	..	1.5	Primary diagnosis, cancer	22	4.8
Unclassified	..	1.0	Unclassified	..	2.8
TIME OF APPEARANCE OF PAIN					
One-half to two hours after food	..	23.0	One-half to two hours after food	..	50.0
Two to five hours	..	77.0	Two to five hours after food	..	50.0
One-half to one hour after food	..	8.0	One-half to one hour after food	..	19.0
Pain at night	..	14.0	Pain at night	..	10.0
Postural ease	..	8.0	Postural ease	..	9.0
LOCATION AND RADIATION OF PAIN					
Epigastrium	..	49.0	Epigastrium	..	52.0
Radiation to back	..	24+	Radiation to back	..	22+
Radiation to left epigastrium	..	4.0	Radiation to left epigastrium	..	10+
Radiation to abdomen and fossae	..	9.5	Radiation to abdomen and fossae	..	9+
Radiation to right epigastrium	..	13.7	Radiation to right epigastrium	..	6.6
CONTROL OF PAIN					
Food or drink, or both	..	75.0	Food or drink, or both	..	66.0
Alkalis	..	38.0	Alkalis	..	33.0
Irrigation	..	11.0	Irrigation	..	9.0
Diet	..	20.0	Diet	..	22.0
Pain continuous from onset of symptoms	..	4.0	Pain continuous from onset of symptoms	..	9.5
Tenderness to touch	..	41.0	Tenderness to touch	..	48.0
Vomiting	..	79.0	Vomiting	..	82.0
Gas	..	77.0	Gas	..	94.0
Hemorrhage by mouth	..	18.5	Hemorrhage by mouth	..	25.0
Blood by bowel	..	18.5	Blood by bowel	..	24.0
Perforation	..	28.7	Perforation	..	26.0
Perforation into pancreas	..	17.0	Perforation into pancreas	..	25.0
Obstruction	..	26.0	Obstruction	..	10.0

Perforation ran about equal in both classes (duodenal, 28.7 per cent.; gastric, 26 per cent.), and of those that perforated, the pancreas received the perforation in 17 per cent. of the duodenal and in 25 per cent. of the gastric cases. Pain to the back, which more or less simulated gall-stone radiation, ran about equal (24 per cent.

duodenal; 22 per cent. gastric) in the two conditions, all cases considered. This clearly accounts for the wide range of suggestion of gall-stones in our cases with gastric lesions.

The effect of diet, as usually prescribed for, or undertaken by, the patient, varied little so far as the comfort it brought to the two types of cases (20 per cent. duodenal; 22 per cent. gastric eased); but the amount, quantity, and kind of food at times so modified the gastric syndrome that their careful consideration helped in the differential diagnosis.

Though apparently so nearly similar are duodenal and gastric ulcers in their final analyses, there are some points that aid in their differentiation. In the whole picture the coming and going of symptoms are not so distinctly seen in gastric ulcer. The pain in the gastric form often comes earlier after food (within one to two hours, in one-half the number), and frequently ceases in a short time or before the next meal. It may return after a brief intermission, to be eased by the next meal, or the distress is such that food is refused lest pain be increased. This is more often the case in gastric than in duodenal ulcer, unless complications are present. Certainly when adhesions and perforations are present in any ulcerative lesion, and clearly more so in those well above the pylorus, pain may begin sooner after food intake. This *early* pain is due apparently to peristaltic movements, tugging at the sensitive adhesions, quite as much or more so than to any acid fluid acting on the chronic ulcer or open wound.

In gastric ulcer a small amount of food more frequently gives ease, while large amounts give immediate pain, and thus patients with gastric ulcer are not so apt to depend on food to give ease, or to so spontaneously state its comforting effect. Acid foods trouble gastric cases less than they do duodenal (and pyloric) cases.

Position is also a greater factor in high than in low ulcer. Pressure, as bending over the arms of a chair, or doubling up on the thighs, gives ease more frequently or prevents pain setting in so severely. Lying on the back or side, or on the stomach, is more often found comforting in gastric ulcer. Therefore, night pain is

not so frequent: (1) perhaps because obstruction is less liable in gastric cases (26 per cent. duodenal; 10 per cent. gastric), or at least the narrowing is less; (2) because the ulcer by the position assumed is relieved of the acid's immediate presence; (3) by the high location of the ulcer the irritating fluid falls below the ulcer or is pressed away from it; and (4) peristalsis eases when the body is at rest, or when pressure is applied. This differential point of position is much more clearly felt in history taking than seems apparent in our final percentages and should, we think, be considered.

Ulcers located toward the greater curvature, ulcers with extensive surfaces, and many saddle ulcers tend to more constant symptoms, thus exhibiting the symptoms of chronic complicated ulcers situated elsewhere. Perforations and adhesions seem more often to affect gastric ulcers than duodenal and, as before stated, peristalsis plays a more important part in pain production when adhesions limit the normal movements.

Eructation of burning sour-water (heart-burn) or of tasteless or salty water (water-brash) is more often mentioned by those who have gastric lesions. Also, bloating and its distress are more frequent in the cases of higher ulcers.

Pain that comes immediately or soon after food intake seems to point to cardiac, fundic, or other extensive ulcerations, perforations, adhesions, or obstruction. Coarse and large amounts of food may increase pain in any ulcer, but more constantly in gastric rather high in position, and high ulcers often seem to have periods of shorter duration (one to five days) and shorter intermissions, or remissions which show a lighter grade of symptoms and tend to constant complaint. Thus the case may run month by month, pain earlier, not constant, and decided food or soda ease; all symptoms varying somewhat as the amount and kind of food, giving one the impression of irregularity, yet constantly of gastric origin. Duodenal or pyloric ulcers more often run an exact course day by day for days or weeks with decided food ease.

However, each case necessarily calls for its own careful consideration, because no symptom, or group of symptoms, can more than

suggest location and often, as our histories show, the gastric case may have the pure duodenal syndrome and the duodenal case may quite as clearly give the gastric type of symptoms. The diagnosis of a gastric lesion being made, the question of its exact location is not paramount. How best to treat the lesion and conserve the patient's health is the vital point.

THE DIFFERENTIAL DIAGNOSIS OF LESIONS OF THE STOMACH AND DUODENUM *

EMIL H. BECKMAN

In the consideration of lesions of the stomach and duodenum it is well to review our methods of diagnosis. Of all the single methods of diagnosis in use at the present time, a carefully taken, well-interpreted history is the most valuable. Practitioners of the old school relied almost entirely for diagnosis on inspection of the patient, palpation, and the history. With the development of laboratory methods there has been a gradual tendency to depend entirely on these aids, rather than to consider them simply as one of many pieces of evidence affording knowledge of an individual case. In the past few years there seems to have been an endeavor on the part of workers in experimental laboratories to find a specific laboratory test for each specific disease. In their enthusiasm to follow up the latest laboratory test, diagnosticians have relied to a great extent on the individual test, and to a corresponding degree have neglected the history, clinical symptoms, and general inspection of the patient. Instead of taking a broad view of the entire subject, obtaining evidence from every source possible, and then summing up the entire case, they have often been biased by the data derived from a single laboratory finding. The carefully recorded case-history affords evidence that can be obtained in no other way. It shows: (1) Previous diseases and previous methods of living may bear on the particular case under consideration; (2) present symptoms and those previously complained of which led

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up to the present condition; (3) that the health of the parents or other members of the family may have affected the patient; (4) that previous illnesses and lowered vitality might have brought about a condition making the present malady possible; and (5) that slight, temporary symptoms several years previous to the time of examination may have been due to one disease, and the later severe symptoms, due entirely to a different disease, may have developed from the former trouble. So that in the final summing up the case history, carefully reported and interpreted, is by all means the most reliable method of diagnosis which we have at the present time.

Analysis of the Contents of the Stomach.—This is one of many special laboratory tests which have been devised for the diagnosis of gastric and duodenal lesions. A great deal of information may be obtained from the gastric analysis, but when the analysis is considered entirely apart from the patient and the patient's history, it has almost no value. High or low acidity depends to a great extent on the condition of the patient at the time the test is made, and may vary from day to day to a remarkable degree. In a patient examined recently at intervals of two days the first time the free hydrochloric acid was 28, and in the other was 0. If the diagnosis were dependent entirely on the amount of free hydrochloric acid, it is easily seen how misleading such observations would be. Further, the amount of acids and ferments in the gastric contents may depend wholly on the general run-down condition of the patient, regardless of the presence of disease in the stomach. I merely mention this point as an illustration that in every case the gastric analysis should be considered, not apart from the other evidence, but merely as one of the various tests which may be added in the final summing up before making the diagnosis.

Other laboratory tests may be mentioned: For example, Salkowski's tests of colloid nitrogen in the urine; the Gräfe Röhmer or hemolysin test in the gastric contents, and the Neubauer and Fischer tests for the presence of polypeptoid-splitting ferment. In addition, we have the presence of the Boas-Oppler bacillus and many others. Up to the present time none of these tests has been

accepted as specific of any definite disease that may be present in the stomach, and yet many of them may be of value when correlated with the other evidence in the case.

The presence or absence of mucus in the stomach may also be mentioned as an aid in diagnosis. Mucus is a protectant, and its absence in the gastric contents means a lack of protection to the mucous membrane; thus a normal amount of acid may irritate the mucous membrane to such an extent as to cause the same symptoms which high acidity causes when mucus is present; in other words, the lack of the natural protecting mucus in the gastric contents will allow irritation to occur, whether from bacterial, chemical, or mechanical causes. Naturally, then, an increase in mucus means irritation, and an attempt on the part of nature to overcome this irritation by the secretion of an excess of mucus.

Examination of the Stomach and Duodenum by the Roentgen Ray.—The roentgen ray has developed wonderfully within the past few years, and its use in the diagnosis of lesions of the stomach and duodenum has become very prominent. Like many of the new tests, the claims made for it are sometimes extravagant. Lesions of the stomach, such as cancer and ulcer, are quite amenable to roentgenologic demonstration by filling the stomach with media opaque to the rays. The demonstration of duodenal lesions is less easy, since the duodenal contents tend to pass through rapidly, and contours are harder to determine than those of the stomach. However, by placing the patient in a favorable position and making multiple plates the duodenal outline can usually be shown. The roentgen signs of disease in the digestive tract may be direct or indirect. Permanent deformity of contour at the site of the lesion is a direct sign. Indirect signs include alterations of tone, peristalsis, and motility, and non-permanent alterations of contour due to spasm. All these signs, especially spasm, may be produced reflexly by conditions outside the stomach. Hence a diagnosis based on indirect signs is hazardous unless the possibility of a reflex cause be eliminated. This is usually done by giving belladonna to physiologic effect and reexamining the patient.

GENERAL CONSIDERATIONS IN THE DIAGNOSIS OF ABDOMINAL LESIONS

Pain.—Pain is a common symptom in a great many abdominal lesions, and it is well to consider its cause, time of occurrence, and character. Pain in the abdomen may occur from two special causes: (1) Contraction of the walls of a hollow viscus, and (2) inflammation plus muscular spasm.

Pain that occurs from contraction of the walls of a hollow viscus due to obstruction is always severe and rhythmic, because of the firm contraction of the muscles in an attempt to dislodge the obstruction, and, later, their relaxation because they are exhausted. Severe renal colic, gall-bladder colic, and intestinal colic due to obstruction are illustrations. No other pain in the abdomen except the pain of perforation compares in severity with this type. The pain of perforation may be as severe for a short period, but it is constant and never colicky.

Pain due to muscular spasm is an attempt on the part of nature to place at rest an inflamed area. This type is more or less constant, but may resemble the intermittent pain of obstruction due to relaxation and contraction of the muscles that are attempting to hold the part immobile, such as occurs in subacute perforations, appendicitis, or peritonitis.

Tenderness usually accompanies pain. As noted by many observers, if an abscess forms (inflammation) in the center of a solid organ, such as the kidney, the liver, or the lung, where there is no muscular action, there is no marked evidence of pain. Only when these inflammatory processes reach the surface of the organ and motion between it and adjacent parts produces muscular spasm in an attempt to limit such motion, does pain occur. Since the stomach and duodenum are organs that do not often become obstructed, severe pain rarely occurs except in perforation, and it is then constant and accompanied by tenderness and rigidity of the abdominal walls. Gastric and duodenal lesions do not produce this type of severe colicky pain, because there is never the complete obstruction that occurs in other hollow organs. Even when the

pylorus is completely blocked, the stomach can empty itself quite readily through the esophagus. Therefore when pain of a severe colicky nature is present, one can be sure that the trouble should be looked for outside the stomach.

Of particular significance is the time of occurrence of pain in the upper abdomen. Pain which occurs immediately upon taking food, especially if accompanied by vomiting, is apt to mean a severe contraction of the stomach, due to reflex conditions and to some disease outside the stomach itself. Pain occurring with periodic regularity between meals, especially if relieved by food, points to a disease in the duodenum or stomach. Constant pain, when not affected by taking food, may or may not be due to disease in the stomach, depending on conditions.

Nausea.—Nausea is not a characteristic symptom of lesions in the stomach or duodenum. There may be slight nausea, but never the prolonged, continuous nausea experienced by patients with an infected gall-bladder or the severe nausea of pregnancy.

Diagnosis of Individual Diseases of the Stomach and Duodenum.—Very few diseases occurring in the duodenum have a definite entity. There are the various relaxed conditions of the duodenum, which are almost always accompanied by a relaxed condition of the other muscular organs, such as the stomach, of which we know very little. These can rarely be diagnosed by any definite chain of symptoms; their cause is unknown, and their cure not understood. Primary cancer in the duodenum probably does not occur; when cancer does occur in the duodenum, it arises in the papilla of Vater, or has invaded the duodenum from the stomach. The symptoms are indistinguishable from those of cancer at the pyloric end of the stomach.

The most common lesion of the duodenum with which we have to deal, and which has a definite symptomatology of its own, is ulcer. Ulcers of the duodenum, pylorus, and pyloric end of the stomach produce the same chain of symptoms, and from the standpoint of the diagnostician should be considered together. While the symptoms are not absolutely identical in all cases, those of a typical case are so well marked that a failure in diagnosis should

rarely occur. The feeling is not really pain, but more of discomfort, gnawing, or burning. The site is usually indefinitely located in the epigastrium, though in some instances a definite point of distress is constant. When there is a particular area of distress, it is more apt to be to the right than to the left of the midline. Pain or distress usually occurs when the stomach is empty, varying from between one to three hours after meals. It is relieved by dilution of the gastric contents, as by food, water, saliva, and almost invariably alkalis. Many patients become addicted to the use of soda without having it prescribed. Pain is usually aggravated by exertion, and is often relieved by absolute rest, especially by lying down. The pain is not usually referred to any great distance from the epigastrium, often to the back, especially in perforations. Low abdominal pain one day, umbilical the next, and following this the epigastric pain that is seen in other conditions is unusual. Graham says: "The longer the period between food-intake and onset of symptoms, the lower the ulcer, as a rule. The more prompt the food ease and cessation of symptoms, the lower the ulcer."

In most cases the appetite remains good, the patient is free from nausea, and enjoys food. The symptoms have a definite periodicity in a remarkably large number of cases; that is, they continue for days, weeks, or months, and then disappear for a corresponding period from no apparent cause. Experience seems to show that a large percentage of cases have a remission of symptoms occurring in the spring and fall months. The symptoms from day to day are almost identical; there is rarely any wide variation. In the earlier stage of the disease distress in the morning is rare, but occurs possibly late in the forenoon, and again in the afternoon. As the disease progresses there is distress at night, which prevents sleep and is relieved only by taking a glass of milk or other food. Vomiting is not common, but there is a regurgitation of sour, acid fluid into the mouth. When vomiting does occur, careful questioning usually reveals the fact that it was induced to obtain relief. In the later stages, when there is continuous spasm or mechanical obstruction of the pylorus, vomiting is more frequent, the pain is more constant, and alkalis and food less likely to give relief.

Hemorrhage occurs in about one-third of the cases of ulcer. It is often severe, and the patient may vomit large quantities of blood or pass large quantities in the stool. The bleeding is not often accompanied with pain, but there is a sense of weakness or prostration. When there is no vomiting, the cause of weakness may become apparent by blood in the stool. At these times it is not uncommon for the hemoglobin to be reduced to an extremely low point—often below 50 per cent. The blood-picture is not altered and is always that of a secondary anemia.

Gastric analysis in cases of ulcer of the pyloric end of the stomach and duodenum in a large percentage of cases shows the total acidity, as well as the free hydrochloric acid, to be higher than normal—often extremely high. The acidity is more likely to be higher in the earlier than in the later stages of the disease. Lactic acid is rarely present in the gastric contents.

Roentgen examination, when carefully done and interpreted by a person of wide experience, should show 85 per cent. or more of gastric and duodenal ulcers. Ulcers of the stomach often produce a niche in the gastric wall, the crater of the ulcer, or an accessory pocket, or an organic hour-glass deformity. Indirectly they may cause a retention from the six-hour meal or spastic manifestations. Deformity of the duodenal outline, especially of its first portion,—the bulb,—is a direct sign of ulcer. This deformity may result from distorting scar of an ancient ulcer, or it may be due simply to spastic contraction excited by the irritation of a small shallow ulcer. A similar distortion may also be caused occasionally by adhesions from a pericholecystitis or other inflammatory processes in the right upper quadrant. Duodenal ulcer may also give rise to indirect gastric phenomena, such as spasm, hypertonus, hyperperistalsis, hypermotility, or six-hour retention.

The symptomatology of ulcer of the stomach is less definite than that of ulcer of the duodenum. The symptoms may be identical, or they may be entirely different. The pain with gastric ulcer is the same in character, but more irregular, is apt to be more constant than in duodenal ulcer, and not so likely to be relieved by taking food. There is not the same periodicity that occurs in duodenal

ulcer. Gastric analysis will show the same high percentage of acidity in most of the cases. Vomiting is more likely to occur. Personally, I believe that these patients are not so likely to be in good flesh as patients with duodenal ulcer. The roentgen ray will show a definite lesion in almost every case of ulcer of the stomach if carefully taken and carefully interpreted.

Perforating Ulcers.—Perforating ulcers of the stomach and duodenum should produce the same symptoms as simple ulcers, with the addition, at some particular time, of pain, tenderness, and muscular rigidity imposed on the old ulcer history. During this time food may cause a great deal of distress and there may be vomiting. Bleeding may also occur, but is not so common as might be supposed. There is no change in the analysis of the gastric contents, but the roentgenogram almost invariably reveals the true condition by showing a pocket or small cavity outside the normal outline of the stomach or duodenum.

Cancer.—As I have already stated, cancer does not occur in the duodenum primarily. Unfortunately, there is no method of making an early clinical diagnosis of cancer of the stomach. A great many cases are ushered in with no previous symptoms of gastric disturbance. A considerable number, however, give a previous history of ulcer or indefinite indigestion. There is no pain in early cancer. Cancer of the stomach, like cancer in other parts of the body, is, in the majority of cases, a painless disease, and unless the growth is near the pylorus, so that it produces some obstruction or is ulcerated, the disease may be entirely symptomless for a long time. Cancer which involves the body of the stomach and is not ulcerated often grows to enormous size without general or local symptoms. I recall one case in which there was no previous history of digestive disturbance, loss of weight, or appearance of disease. The patient consulted a physician on account of his inability to swallow solid food. On examination his entire stomach was found to be a mass of cancer, and it was with the greatest difficulty he could be convinced that his condition was inoperable.

When cancer of the lesser curvature and pylorus has advanced to the stage where symptoms are produced, there is constant distress

in the stomach, associated with loss of appetite, loss of strength and weight, and anemia, which does not occur with simple ulcer. This chain of symptoms with low acidity should make one suspicious of cancer of the stomach. It should be remembered that gastric cancer is very common, and that probably one-third of all cancers in the body occur in the stomach. Patients presenting themselves with cachexia, a palpable tumor, and marked loss in weight are so far advanced that nothing can be done. The localized cancer on the surface of the body presents no symptoms, and is discovered only by inspection and palpation. It is probably true that early cancer of the stomach likewise produces no symptoms. Cancer of the stomach can be diagnosed extremely early by the roentgen ray. One is more and more convinced that diagnosis can be made earlier by an intelligent roentgen examination than by any other means. A small growth in the stomach will show an irregularity in the outline of the stomach, while an infiltrating growth that does not produce irregularity can be discovered on screen examination by an absence of the peristaltic waves at this point. The roentgen examination is of the greatest value in determining the operability of cancer of the stomach. Its use will save many needless exploratory operations.

Syphilis of the Stomach.—Much has been written recently on syphilis of the stomach, and one is led to believe that this is a very common condition. However, considering the number of syphilitic patients, it is an extremely rare condition and one not easily recognized. The symptoms seem to be those of an indefinite history of ulcer, with an almost complete absence of gastric ferments and acids. In such cases one should be suspicious of syphilis and the Wassermann test should be made: If this is positive, and the condition of the stomach is entirely relieved with antisyphilitic treatment, it is fairly safe to make a diagnosis of syphilitic disease of the stomach. It may not, however, be an actual lesion, but simply a condition due to the general infection. Many of the contracted hour-glass stomachs are due to partially healed lesions of syphilitic nature. These patients give an indefinite gastric history covering a long period of years, and the diagnosis is made largely from the

roentgenogram. At this stage the patient can be relieved only by surgical means.

I shall not discuss the various types of gastric conditions known as motor inefficiency, and the various types of symptoms associated with a diminution of the secretions of the stomach, for the reason that very few of these are really diseases, but are dependent on some general reduction of the patient's vitality, and can be helped only by its correction. No two internists agree on any classification or pathologic basis for these conditions; consequently no definite symptomatology or treatment can be outlined.

GASTRIC ULCER *

WILLIAM J. MAYO

Ulcer of the stomach is a more serious condition than ulcer of the duodenum, but fortunately is less frequent, our statistics showing 27 of the stomach to 73 of the duodenum. Gastric ulcer is the more serious because of the resulting deformities which permanently cripple the stomach and, when extensive, interfere with gastric digestion and motility. The mechanical condition can be relieved by operation, but the physiologic function of the stomach is often more or less permanently impaired. In ulcer of the duodenum the gastric motor and secretory functions are not disturbed and, in the presence of gastro-enterostomy, are continued in an efficient manner.

Acute perforation in ulcer of the stomach is less common than in ulcer of the duodenum, but in the former there is less probability of the ulcer being protected by adhesions. The gastric capacity is large, so that considerable contents may escape. Since the contents are relatively much less sterile than in the duodenum, there is a greater chance of perforation producing general septic peritonitis. When operations are performed for acute perforation of gastric ulcer, the opening will often be found in the center of a large calloused area, making closure difficult.

Hemorrhage occurs in both gastric and duodenal ulcers with about the same degree of frequency and danger, but in the stomach it may have other origin. So true is this that the large majority of severe hemorrhages from the stomach which are not preceded or followed by the ordinary signs and symptoms of ulcer are not

* Read before the Section on Surgery, General and Abdominal, at the Sixty-sixth Annual Session of the American Medical Association, San Francisco, June, 1915. Reprinted from the Jour. Amer. Med. Assoc., 1915, lvi, 1069-1073.

due to ulcer, but the result of some type of gastro-intestinal or hepatic poisoning.

There is, in gastric ulcer, the ever-present danger of cancer developing on the ulcer, a danger to which duodenal ulcer does not appear to be liable. Finally, the operative procedures which must

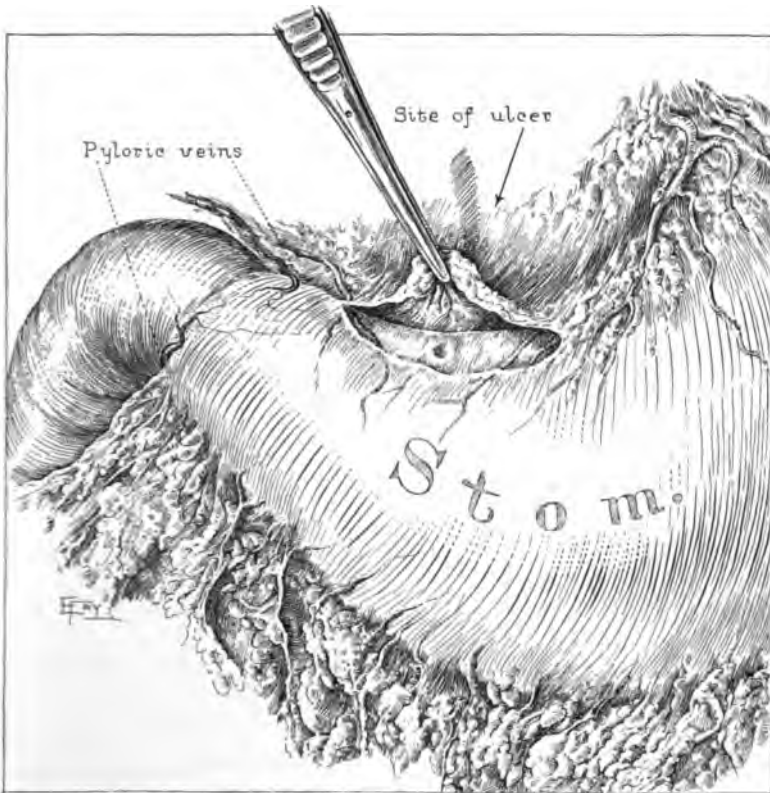


Fig. 70.—Musculoperitoneal flap with gastrohepatic omentum and adhesions raised, exposing the ulcer
Note pyloric veins.

be carried out for the relief of gastric ulcer are more serious than in duodenal ulcer; there is, moreover, a somewhat larger mortality and a somewhat smaller degree of certainty of cure. The history and clinical symptoms of a typical duodenal ulcer are so distinctive that, as Moynihan¹ has pointed out, the diagnosis might be made

by correspondence; but many duodenal ulcers are not typical in their symptomatology, and this is even more true of gastric ulcers. Therefore, in a very considerable percentage of cases, an exact differential diagnosis between duodenal and gastric ulcer could not be established until the advent of fluoroscopy. In duodenal ulcer hyperperistalsis of the stomach and deformities of the cap and, if obstruction exists, bismuth retention, give a typical appearance and are almost as typical as the roentgenographic appearance of the niche in gastric ulcer and the appearance of hour-glass and other deformities.

Usually the pain in duodenal ulcer comes later and radiates from the epigastric midline to the right; in gastric ulcer it may radiate to the left. When posterior adhesions of gastric ulcer exist, especially when the crater involves the pancreas, pain in the back is a frequent symptom.

Gastric ulcer is more frequent in men than in women—71 males to 29 females—and is single in the larger number. The proportion in duodenal ulcers is 83 males to 17 females.

The occurrence of carcinomatous change in gastric ulcer has been a moot question from those who believe, with Aschoff,² that it is a comparatively rare phenomenon, to those like Moynihan,¹ Wilson,³ MacCarty,⁴ and others, who believe that it is a very frequent condition. The opinion of the postmortem pathologist who studies only the end results has no such value as the opinion of the clinical pathologist who has an opportunity to make the examination during the life of the patient, an opportunity which the operative removal of gastric ulcer and carcinoma has made possible. Fütterer⁵ pointed out the relation of fishhook ulcer to gastric carcinoma and presented proof that malignant change actually took place. Wilson³ and MacCarty,⁴ from the study of a large number of specimens, showed that it was not the base but the overhanging margin of the ulcer which became carcinomatous. A review by Wilson⁶ of the later histories of 19 cases in which a gastric ulcer had been excised and diagnosed as probable early malignancy, in 1909, has been of very great value in clearing up the question, as four of these patients have since died of gastric carcinoma. Accepting as

correct Aschoff's³ criteria that if the base of the ulcer is carcinomatous the ulcer has been carcinoma from the beginning, Wilson was able to show in the excised specimens that the carcinoma had developed on the margin of the ulcer, as the base was of cicatricial tissue and free from cancer.

A study of the cases reported by von Eiselsberg⁷ is interesting.

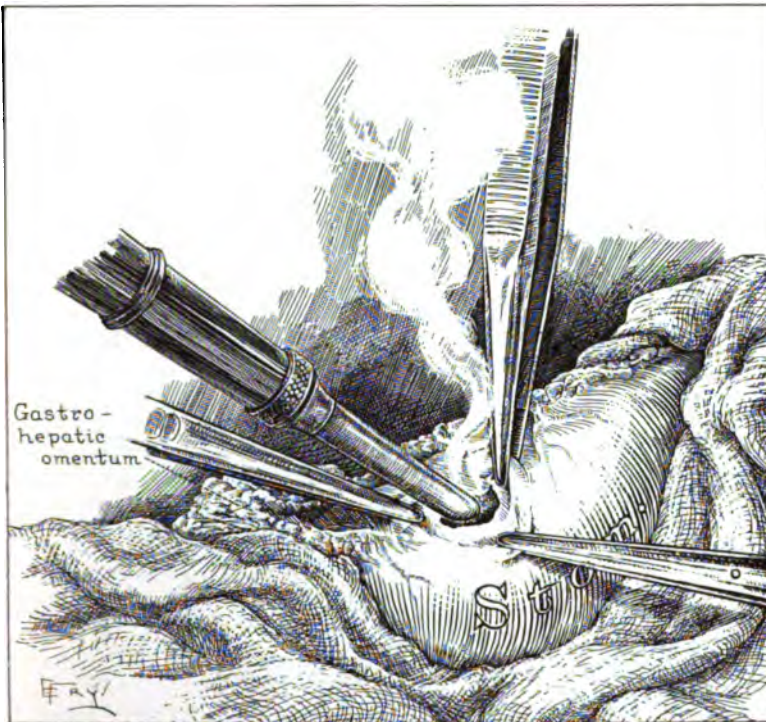


Fig. 71.—Excision of the ulcer by means of the Paquelin cautery.

He shows, from the ultimate history of patients operated on in his clinic for gastric ulcer, that 10 per cent. have since died of cancer of the stomach. The differentiation between ulcer of the stomach and duodenum was not so well established at the time these operations were made as now, and the series showed few duodenal ulcers. It may be surmised that a percentage of the ulcers near the pylorus

were duodenal, not gastric, and yet had been classified with the gastric. Since a duodenal ulcer rarely undergoes malignant change, this would increase the relative percentage of secondary

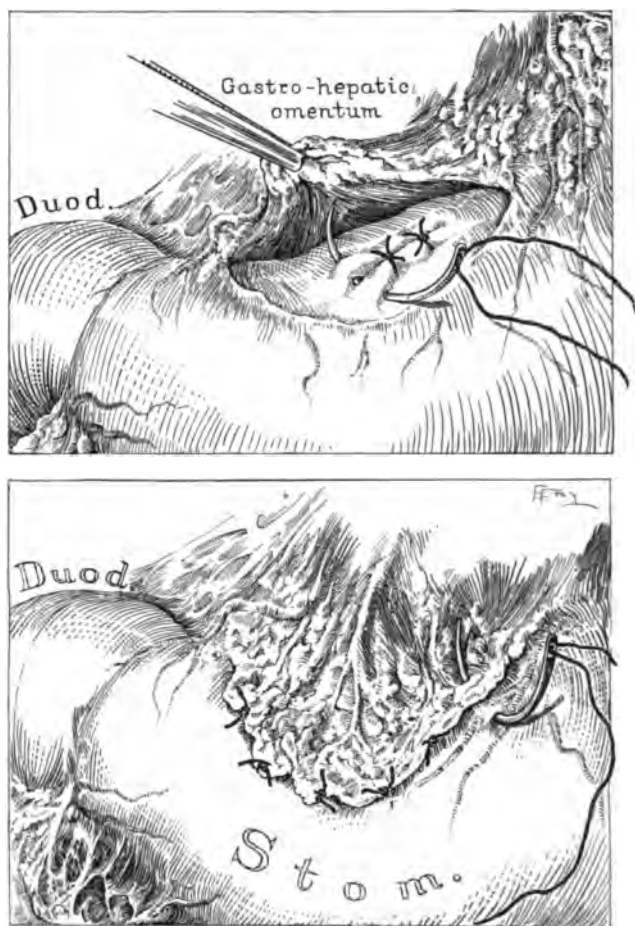


Fig. 72.—Upper figure shows closure of the gastric opening with chromic catgut and interrupted silk sutures. The lower figure shows the flap reappplied.

gastric malignancy by whatever that error may have been. Analyzing von Eiselsberg's⁷ statistics still further, it is found that 13 patients died with carcinoma following operation for ulcer.

The total number of deaths was 41. In other words, 32 per cent. of all the deaths following operation for gastric ulcer were from gastric cancer. Recent data from the clinics of Payr, Perthes, Küttner, and others show the same results.

Wilson³ has contributed materially to the theory that detached fragments of functioning gastric epithelium buried in the ulcer by scar tissue may be the starting-point of carcinomatous change. While it is not justifiable to say that all carcinomas of the stomach have their origin in ulcer, there is sufficient evidence to show that a preceding lesion in the gastric mucosa is practically always present before carcinoma develops. The prevailing skepticism on this point is not justified by the facts, and tends to prolong medical treatment of chronic cases which would be more promptly treated by the surgeon were the carcinoma liability in addition to the ulcer risk and disability better understood.

Opinions as to the medical cure of ulcers are based on the frequent cessation of symptoms, which, for that matter, occurs with or without treatment. When supposedly cured patients are operated on during the quiescent interval, the ulcer is not found to be cicatrized, but unhealed. The roentgenogram shows the same condition. While no one would contend that every gastric ulcer should be surgically treated, we at least should agree that if permanent cure does not take place within a reasonable period, other things being equal, the patient should have surgical treatment.* * * * *

PYLORIC ULCER

The location, size, and relations of gastric ulcer are extremely important from a surgical standpoint. The conditions created vary from the simple problems presented by a pyloric ulcer with obstruction, to those more complex problems represented by hour-glass contractures and extensive posterior ulcerations involving the pancreas. Ulcer of the pyloric end of the stomach and antrum should not be mistaken for duodenal ulcer. When ulcer occurs in the terminal one and one-half inches it is prone to develop a tumor, which, with the edema and obstruction, may and probably will be mistaken for carcinoma. When operating during an exacerbation,

* William J. Mayo, "Chronic Duodenal Ulcer," p. 240.

an unusual amount of hypertrophy and edema in the immediate vicinity of such an ulcer will be found. The mass can often be felt through the abdominal wall on palpation. Cases are frequently reported in literature in which the two-stage operation for cancer of the stomach was planned, and after a preliminary gastro-enteros-

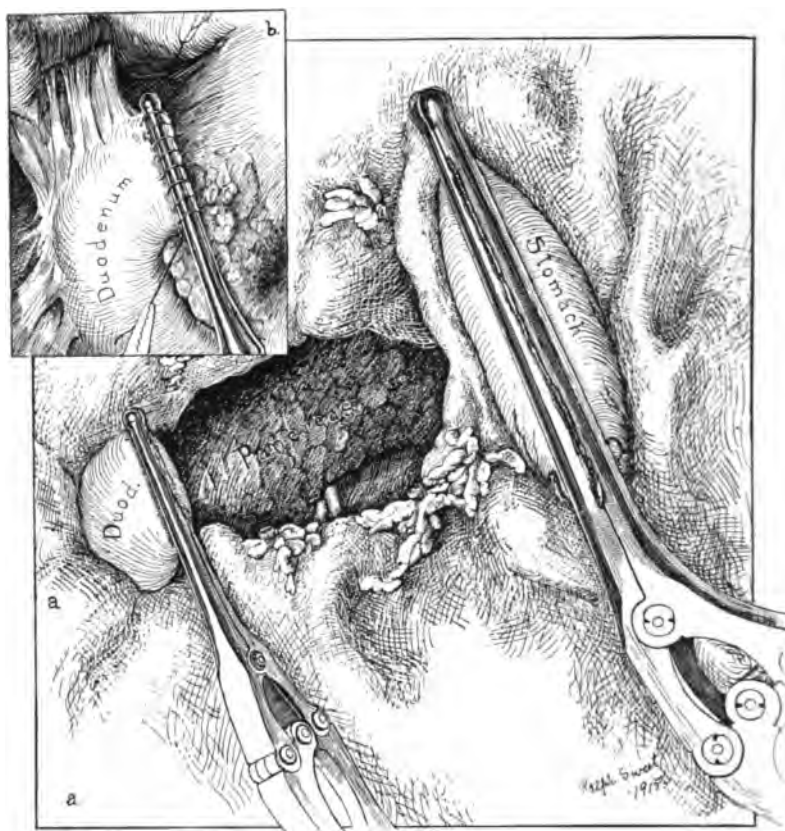


Fig. 78.—Pyloric half of stomach removed; a, a, Ends in crushing clamps; b, sutures placed for closing ends of duodenum.

tomy the tumor completely disappeared. It is reported that one of Billroth's early patients on whom gastro-enterostomy was done for supposed carcinoma of the stomach lived twenty years following operation. In our earlier experience several patients in whom a gastro-enterostomy was done for what appeared to be a fixed,

inoperable malignant growth of the pyloric end of the stomach, clinically not distinguishable from cancer, lived five years or more following simple gastro-enterostomy. With increasing experience one finds that there are differentiating signs between pyloric cancer

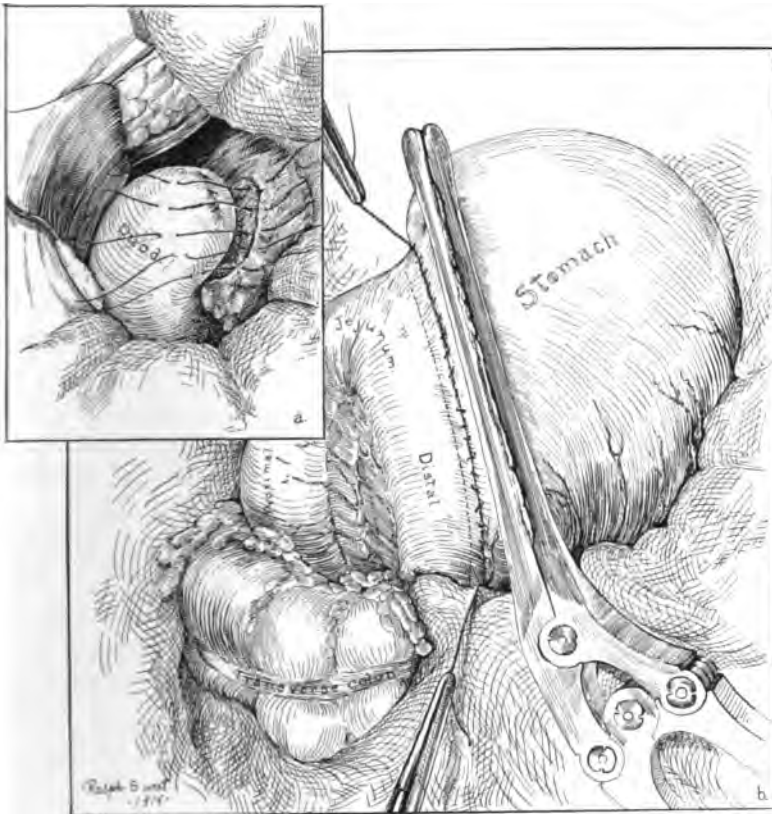


Fig. 74.—*a*, Sutures in position for final closure of duodenum; *b*, jejunum, close to its origin, brought through an opening made in transverse mesocolon and sutured with interrupted silk sutures to posterior wall of stomach. Dotted line along jejunum shows proposed incision for gastro-intestinal anastomosis. Crushing clamp to be removed to open up gastric cavity for the anastomosis.

and ulcer when the tumefaction is exposed. A greater amount of edema, more extensive adhesions, and more fixation occur in ulcer than usually occur in cancer of the same size. Ulcer does not present those little separated carcinomatous foci in the vicinity of the

growth from dissemination just underneath the peritoneum. The glands are usually enlarged in both ulcer and cancer, and the removal of such glands which do not show cancer is unfortunately not conclusive, because glands enlarged from sepsis often exist in connection with cancer, but in which the glands themselves have no malignant cells. MacCarty and Blackford⁷ have called attention to the fact that the size of a regional lymphatic gland is no criterion of the presence or absence of gastric cancer.

In the differentiation between pyloric ulcer and ulcer of the duodenum the pyloric veins are an important diagnostic aid (Fig. 70). Above and below the pylorus short, stumpy veins come up on each side and give off one or more veins, sometimes anastomosing across the anterior surface, sometimes ending in a little spray of vessels. Once having observed the peculiarity of these pyloric vessels, which are quite different from those in any other situation on the stomach, differentiation is easy.

The Rodman¹⁰ operation of pylorectomy and partial gastrectomy for this particular group of ulcers is remarkably well adapted to give relief; it removes the cancer liability and also a considerable portion of the acid-forming part of the stomach, and this removal is of importance in reducing the possibility of the production of that rare but serious after-result of gastro-enterostomy, the jejunal ulcer. It should be remembered, however, that the mortality of the Rodman operation is somewhat greater than simple gastro-enterostomy, and that simple gastro-enterostomy will usually cure the patient. The Rodman operation, therefore, should be reserved, first, for those patients in whom the physical conditions are such that the operation can be performed with a minimum risk, and, second, for those patients in whom the possibility of cancer amounts to a probability, so that the increased risk of the operation will be more than counterbalanced by the benefits to be derived from it.

ULCER OF THE LESSER CURVATURE AND ANTRUM

The work of Forssell¹¹ in showing the gastric tendon of the lesser curvature of the stomach is very important in relation to

ulcer of the lesser curvature, and explains why the simple excision of an ulcer without gastro-enterostomy may fail to effect a cure even though the pylorus be not obstructed. It would appear that the portion of the greater curvature of the stomach which corresponded in its musculature to the lesser curvature at the seat of the ulcer is often permanently crippled by the ulcer, and that the condition was not overcome by its excision. A considerable percentage of our cases of ulcer of the lesser curvature in which excision had been done later required gastro-enterostomy, and this operation is now performed at the time the excision is made. Two deaths have occurred after excision of a simple ulcer of the stomach, from continuous hemorrhage coming on in the second week. The first week following the excision the patients did well; in the second week there was hemorrhage into the stomach, at first not serious, but gradually becoming severe. As a last resort in each case, gastro-enterostomy was done, but without avail. It was shown at postmortem that the bleeding did not come from definite vessels. The mucosa had failed to unite and had widely retracted, leaving the muscular coat exposed in the lumen of the stomach, and this was the source of the oozing blood.

Following these two unfortunate results, Balfour¹² (Figs. 71 and 72) began the use of the actual cautery to destroy the ulcer. His method is as follows: The peritoneal and muscular coats are dissected back from the ulcer in the shape of a flap. Then the Paquelin, heated to a dull red (just hot enough so that it will not stick), is pushed through the ulcer, gradually heating the entire calloused area. The cautery opening is closed with chromic catgut and interrupted silk, the flap of peritoneal and omental tissues is replaced, and, finally, gastro-enterostomy is performed. Experiments which Balfour and Mann conducted on dogs showed that the cautery sealed the gastric mucosa to the muscular tissues and that the scar was almost imperceptible. Experience with this method in a very considerable number of cases has steadily given good results. When there is suspicion of malignancy, a bit of tissue is excised for microscopic examination before using the cautery. The use of the cautery in these cases, however, destroys the ulcer and the diseased

mucosa in its vicinity so thoroughly and coagulates, as shown by Percy, tissues beyond to such an extent that one might expect the method would be as effectual as local excision against early malignant disease. Of course, if malignancy is shown to exist, resection is indicated.



Fig. 75.—Entire end of stomach anastomosed to jejunum posteriorly with interrupted silk and a through-and-through continuous catgut suture which is being continued on to anterior surface.

In some cases in our clinic in which the cautery and gastro-enterostomy were combined the pylorus was also blocked to force the food out of the gastro-enterostomy opening. The results have been excellent in either case, and blocking the pylorus has not seemed to have added anything of value to the operation.

LARGE ULCERS OF THE BODY OF THE STOMACH

Large ulcers occupying the body of the stomach, when the callus and ulcer are too large for the cautery operation of Balfour,¹² are best treated by the sleeve resection, that is, the removal of a segment of the stomach including the ulcer, and an end-to-end anas-



Fig. 76.—Operation completed and end of stomach drawn completely through opening in transverse mesocolon. Margin of opening sutured to gastric wall.

tomosis of the two fragments. This shortens the stomach considerably, but gives an excellent permanent result. Just why this operation, in which the corresponding part of the greater curvature is removed at the time the ulcer is excised, should leave a stomach with good motility while excision of the ulcer without removal of

the segment of the greater curvature leaves it with poor motility is an interesting conjecture.

The most serious ulcers are those of the body of the stomach involving the posterior wall. These ulcers are usually of large size and often involve the pancreas. At times there is an ulcer with a foul crater of considerable size containing food remnants and in which it is extremely difficult to tell whether or not malignant disease is present. In a general way it can be said that where the actual crater of the ulcer is larger than a silver dime the majority of gastric ulcers will prove to be undergoing malignant change. On the posterior wall of the fundus of the stomach this is not so generally true, for, while many of these ulcers are malignant, some extensive ulcers are benign. For such ulcers, if not too large, the transgastric operation¹³ will be found satisfactory. The anterior wall of the stomach is opened, the ulcer excised, and the gap sutured from within the stomach. The base of the ulcer may be pancreatic tissue; if so, it can be shaved off with a sharp knife until all the exposed part of the callus has been removed, or it may be destroyed with the actual cautery. If it is possible to gain access to the posterior wall of the stomach, a few musculo-peritoneal sutures may be placed to protect the sutures applied from within the gastric cavity, but experience has shown that these are not essential. We have, however, taken the precaution to carry a strip of folded rubber tissue to the pancreatic lesion after covering it with omental grafts. Since in none of these cases has there been any discharge following such drainage, it can be looked on as unnecessary. I am convinced, however, that the more extensive ulcers in this situation are better treated by radical removal of the entire distal end of the stomach, including the ulcerated and contracted area, and then the end of the gastric pouch anastomosed directly into the side of the jejunum. This furnishes perfect drainage, gets rid of the entire acid-forming part of the stomach, and insures the patient against recurrence. Comparatively few cases are sufficiently serious to warrant so extreme a procedure, but in several instances, after the failure of less radical means to give relief, and especially in the presence of secondary jejunal ulcers, I have adopted this plan with great satisfaction.

HOOR-GLASS STOMACH

The hour-glass stomach, if a single loculus, may be treated by gastrogastrostomy after the Watson method or by the sleeve resection just described. We have found the results of either of these operations satisfactory. A gastrogastrostomy which is planned in a general way after the Finney gastroduodenostomy will give excellent results. A considerable number of hour-glass stomachs have secondary obstruction in the vicinity of the pylorus, or they are associated with duodenal ulcer. In either case gastro-enterostomy in addition to the treatment of the hour-glass condition is necessary (Figs. 73, 74, 75, 76). Where several loculi exist, increasing the lumen of each by a plastic operation of the Heineke-Mikulicz type, so that they shall be converted into one large cavity, and then making a gastro-enterostomy, is most efficient.

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FOREIGN BODIES SWALLOWED BY AN INSANE WOMAN*

DONALD C. BALFOUR

The practice, by professionals, of swallowing foreign bodies, and the mania for doing so by the insane, have contributed to medical literature instances of the most grotesque assortment of articles having been retained in the stomach for long periods without injury to the mucous membrane and without producing symptoms. The case I shall report is somewhat novel, in that the patient exhibited a preference for one article, namely, teaspoons. The limit of this woman's capacity, had her habit not been discovered and interrupted, can only be conjectured. The nurse in charge of a ward at the Rochester State Hospital by chance saw a teaspoon disappear into the woman's mouth. A roentgenogram was immediately made, which showed apparently three or possibly four spoons in the stomach. The woman, who was twenty-nine years of age, was evidently in perfect physical health, and, as far as could be determined, had suffered no distress or inconvenience from the presence of the spoons.

September 1, 1915, a gastrotomy was done and seven teaspoons, instead of the supposed three or four, were found. They were lying together "spoon fashion" (which explains the roentgenogram), and a hairpin, some straw, and small pieces of twigs lay around them. After removing the spoons and débris the stomach was carefully examined for possible injury. However, other than a rather large prolapsed organ and a hypertrophied and congested mucous membrane no evidence of injury was found.

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The spoons, which were of plated Utah metal, were not bent and showed no erosion. They were a little larger than a standard



Fig. 77.—Foreign bodies swallowed by an insane woman.

teaspoon, being six inches in length and one and one-half inches across the bowl. The patient made an uneventful recovery (Fig. 77).

THE ROENTGENOLOGIC DIAGNOSIS OF DUODENAL ULCER *

RUSSELL D. CARMAN

A sharp divergence of opinion has existed among roentgenologists as to the relative importance of certain manifestations noted in association with duodenal ulcer. This discordance, I believe, can be considerably lessened, if not wholly removed, by a frank presentation of the subject.

Deformity of the bulb, first pointed out by Lewis Gregory Cole as a roentgenologic sign of duodenal ulcer, and which has received the unqualified indorsement of others, has been regarded with skepticism by some of us. Heretofore, I have been among those who could not share Cole's enthusiasm, and have freely expressed the opinion that bulbar deformity, though of occasional diagnostic value, should be ranked among the secondary signs. During the past year my experience with this sign has led me to regard it with much greater favor. Though I would not, even yet, place exclusive reliance upon cap distortion for diagnosis, I believe it only fair to say that I now consider this sign to be one of our best indices, capable of practical application, and well worth searching for in those cases in which the simpler methods of examination fail to establish or exclude the presence of duodenal ulcer (Fig. 73).†

On previous occasions I have called attention to the following handicaps to the diagnosis of duodenal ulcer on bulbar deformity:

1. That irregularities of the duodenal outline are not pathog-

* Read before the American Roentgen Ray Society, Atlantic City, September 22-25, 1915.

† All the illustrations herewith shown are from operated cases. All had duodenal ulcers except the cases illustrated in Figs. 78, 80, and 83.

nomonic of ulcer, or even of a duodenal lesion, and that such distortion may be due to adhesions from some other process, such as pericholecystitis, or possibly to spasm excited by a remote lesion.

2. That some ulcers of the duodenum do not produce an organic distortion which is roentgenologically demonstrable.

3. That adequate filling of the duodenum with the opaque meal, and hence its effective visualization, is not always easily obtained, since it depends on the ratio between the amount passing the



Fig. 78.—(130,272.) Normal stomach and duodenal bulb.

pylorus and the rate of duodenal evacuation, which is not controlled by any distal sphincter.

Each of these objections I still consider valid. How, then, can they be reconciled with my present belief that bulbar deformity is one of our best indications of duodenal ulcer?

In the first place, while irregularities of the duodenal contour may be sometimes produced by pericholecystitis and other adhesion-producing lesions, or perhaps by spasm reflected from dis-

tant sources, deformity due to such causes is much less common than deformity resulting from duodenal ulcer. A knowledge of the clinical history will often put the roentgenologist on guard for these possibilities. But distortion of the duodenal bulb by extraduodenal adhesions is probably less frequent in fact than in theory. I can recall at least one instance in which the duodenum was matted in adhesions, yet showed a normal bulbar contour on the plate.

In the second place, while some duodenal ulcers produce a scar-distortion of the duodenal lumen which can be readily seen on the roentgen plate, there are others in which the organic deformity is so slight that it cannot appreciably distort the barium shadow. I refer especially to the small mucous or slit ulcers which are occasionally found at operation. In these there is only a slight inflammatory thickening, which is not visible when the duodenum is exposed. The surgeon recognizes the ulcer by the sense of touch and by stippling produced by rubbing the serosa with the finger or gauze. The disproportion between the amount of distortion that Cole was demonstrating on his plates, and the amount that I was customarily seeing at operation, made it most difficult for me to accept his theory. However, when we began to employ the serial method our plates also frequently showed bulbar deformity greater than could be explained by the pathologic condition seen at operation, when the patient was relaxed by the anesthetic. The deformity of the bulb in such cases is, I am satisfied, largely the result of spasm, exactly similar to the incisura of gastric ulcer or the spastic distortion of the pars pylorica so often seen associated with prepyloric ulcers. On this hypothesis it is possible to understand why the distortion of the bulbar shadow is out of proportion to the organic alteration, and of a more exaggerated character. Absence of spasm would also explain why, in some cases of ulcer, no cap deformity can be demonstrated—an experience which has happened to others than myself.

In the third place, with the patient standing, the position we heretofore chiefly employed, the duodenum frequently cannot be well visualized because the barium passes through it too rapidly.

But with the patient prone or on his right side, the duodenum can often be filled and shown more effectively. Lippman,* working with Holsknecht, found some advantage in using the "distinctor" for blocking the duodenum in order to render it visible during the screen examination. With patients whose abdominal wall is relaxed we are sometimes able to dam up the duodenal contents by manual pressure during the vertical screen examination. However, the recumbent position will usually bring out the duodenal contour better for both screening and plating. Even by this method there is frequently considerable difficulty in obtaining a well-filled bulb, and repeated plating or a second examination is sometimes necessary.

Regardless of explanations, theories, and opinions, the fact remains that for a year past we have satisfactorily tried out the serial method, though modifying it in some particulars. During this period our diagnoses of duodenal ulcer have been confirmed at operation with fewer exceptions than before, and fewer ulcers have escaped diagnosis. We have not limited ourselves to this method exclusively, but have simply added serial roentgenography of certain cases of suspected duodenal ulcer to our routine screen and plate examinations. We have found that it is not always necessary to make multiple plates. Under favorable circumstances the fact that the bulb is of normal contour can be determined by the screen inspection, with the patient either upright or recumbent. Conversely, constant bulbar deformity can occasionally be clearly demonstrated in the same manner. In making serial plates the number made depends upon the result. In many cases the examination can be terminated when as few as a dozen plates show identical and characteristic bulbar deformity, or when any one plate shows a normal bulb.

The definite bulbar deformities more or less characteristic of duodenal ulcer are of various types, among which the following are noteworthy:

1. General distortion with sharply outlined projections and

* Lippman, C. W.: "The Duodenum; a Roentgen Study," *Surg., Gyn. and Obst.*, 1914, xix, 724.

incisura-like indentations, giving the cap the semblance of a miniature pine-tree or a bit of branched coral (Fig. 79). This sort of bulb almost always means duodenal ulcer. The distortion is largely organic; if partly due to spasm, the latter element is persistent and unvarying. In some cases of this type the whole contour of the



Fig. 79.—(128,344.) Marked deformity of bulb. Large calloused ulcer, anterior wall of duodenum.

bulb is deformed (see Fig. 79); in others only one border or the basal portion is decidedly irregular. That a pericholecystitis or adhesions from other inflammatory processes in this vicinity may produce a similar deformity must be admitted and should be kept in mind as a possibility (see Fig. 80). Cancer of the duodenum is so rare that it should be thought of last of all (Fig. 81).

2. The niche type. The excavation of the ulcer is visible as a barium-filled recess in the bulbar chamber. It varies from a wheat-grain to a pea, or larger, in size, and its barium content is usually denser than that in the rest of the bulb (see Fig. 81). The niche may or may not be accompanied by spastic incisura (Figs. 82 and 83).



Fig. 80.—(126,815.) Definite distortion of bulb, constant in series. Diagnosed roentgenologically and clinically as duodenal ulcer. At operation the gall-bladder was found buried in a mat of adhesions which bound the duodenum to the liver. No duodenal ulcer found.



Fig. 81.—(128,007.) Niche type of duodenal ulcer.

3. The incisura type of deformity. The incisura may be single or bilateral. It is usually small, but sharply outlined, is evidently spastic, and presumably occurs in the plane of the ulcer (see Fig. 82). As a rule, it is significant of ulcer, but we have had one case in which delicate adhesions confined to the anterior duodenal wall were the cause (see Fig. 83).

4. A fourth variety is a bulb represented by a very small mass of barium (see Fig. 84). There is no particular irregularity of contour,



Fig. 82.—(122,201.) Incisura type of bulbar deformity.

but the bulbar shadow is abnormally small. Occasionally it is produced by a stenosing ulcer. The duodenum of a steer-horn stomach, which often turns rather abruptly backward, may also give this sort of shadow in the anteroposterior view. In other instances there is perhaps a scant exit of barium through the pylorus, or rapid duodenal clearance, or both. When due to obstructing ulcer, six-hour retention, hyperperistalsis, and antral dilatation are also present. In the absence of these signs continued plating should finally show a normal bulb.



Fig. 83.—(128,638.) Hour-glass duodenum. Roentgen diagnosis: duodenal ulcer. Operation: Cholecystitis, with a few delicate cobweb adhesions. When these were stripped off, the duodenum assumed a normal appearance. No ulcer found.



Fig. 84.—(125,446.) Small, rounded cap, constant in series. Stenosing ulcer of the duodenum.

In a small percentage of the cases the bulb shows indefinite shading off here or there, but without sharply outlined or permanently localized irregularity. In other words, while no normal filled cap is seen on any plate, the observer feels quite uncertain whether the bulb is actually irregular or is only partially filled. By repeated plating or reexamination at a subsequent time a completely filled cap, usually of normal contour, may be obtained.



Fig. 85.—(111,247.) Diverticulum of duodenum, above a stenosing ulcer.

What, then, shall be done with the other roentgenologic signs of duodenal ulcer? Shall they be discarded as worthless? By no means. Let us invoice them again:

1. Duodenal diverticulum.
2. Gastric hypertonus, hyperperistalsis, and hypermotility.
3. Six-hour gastric residue.
4. Antral dilatation.
5. Gastrosperm.

Either true or false diverticula result occasionally from duodenal

ulcer. In the true type all the coats of the duodenum are preserved in the sacculum (Fig. 85). True diverticula are relatively rare, being found in less than 1 per cent. of the total number of ulcers. False diverticula result from perforation of the ulcer and excavation of adjacent tissue. These are somewhat more common than true diverticula. Both types are recognizable roentgenologically, and, when present, constitute an excellent sign of duodenal ulcer.

The triad of "hypers," namely, hypertonus, hypermotility, and hyperperistalsis, was given early recognition by the pioneers in roentgenology as being more or less valuable indications of duodenal ulcer. These phenomena are seen in various combinations, often all together. Gastric hypertonus as an accompaniment of duodenal ulcer may be explained upon either one of two grounds: First, it may occur as a spastic increase of tone which stops short of the general reflex gastrosplasm, familiar to us as a sequence of numerous conditions outside the stomach. Second, it may result from the effort to overcome beginning stenosis of the duodenum. Whatever the reason be, hypertonus is seen with the majority of duodenal ulcers, and perhaps more frequently in this than in any other condition. True, it occurs also as a normal feature of the steer-horn stomach, seen now and then in persons of the broad habitus, and is an occasional accompaniment of various pathologic conditions within and without the stomach.

Gastric hyperperistalsis is notable in a large proportion of cases—perhaps 60 per cent. or more (Fig. 86). It varies in intensity from a slight exaggeration of wave-depth to a tempestuous energy of contraction, depending upon the degree of obstruction. A distinctive feature is the regular succession and symmetric correspondence of the waves on both curvatures. Three or four pairs may be seen in progress at once, whereas with the media which we employ only one or two pairs are commonly seen normally. Hyperperistalsis is often intermittent in character, periods of activity alternating with periods of rest. Its appearance is also sometimes a little delayed after the stomach is filled—not usually, however, beyond five or ten minutes. Of course, we are all aware that the phenomenon of hyperperistalsis is not limited to duodenal ulcer. It may excep-

tionally accompany lesions of the gall-bladder or appendix, or be seen normally in the hypertonic steer-horn stomach, but in any of these, as a rule, is less pronounced than in duodenal ulcer. The exaggerated peristalsis which can sometimes be elicited by massage of the epigastrium or palpating a tender appendix soon dies away



Fig. 86.—(115,616.) Large normal stomach showing hyperperistalsis (three waves). Retention of half the barium motor meal after six hours. Diagnosis, duodenal ulcer.

when the stimulus ceases. Obstructing pyloric and prepyloric lesions are sometimes attended by hyperperistalsis, but this is nearly always of a disorderly character as to the depth and sequence of the waves, and the greater curvature is chiefly affected. This sort of exaggerated hyperperistalsis sometimes accompanies duodenal perforation. In estimating the degree of peristaltic

activity it is to be remembered that peristalsis is more lively in the recumbent than in the standing posture, and that it is influenced by the character of the opaque meal. Comparisons should be made under identical circumstances.

A logical result of hypertonus and hyperperistalsis is hypermotility, if no obstruction has been produced by the ulcer. Rapid clearance of the stomach is also furthered by the free patency of the pylorus, so often observed. During screen-inspection the barium is seen passing out into the duodenum in a copious stream, not quite so voluminous as that remarked with the gaping pylorus of cancer, but larger than normal. The head of the six-hour meal, instead of being in the cecum or ascending colon, as normal, may be in the transverse or even in the descending colon. Again, it is to be conceded that hypermotility is not peculiar to duodenal ulcer, and that it is a common effect of gastric cancer, achylia, and the diarrheas. If these be excluded, as can usually be done by considering the salient roentgenologic and clinical facts, a pronounced hypermotility should strongly suggest the possibility of a non-obstructing duodenal ulcer being present.

On the other hand, more than one-fourth of these ulcers are sufficiently obstructive to produce a six-hour retention in the stomach. The testing of motility by a modification of Haudek's double-meal method has become an indispensable part of our routine. A six-hour retention in a stomach with an unbroken contour, that is to say, without any roentgen evidence of gastric ulcer or cancer, should, first of all, suggest duodenal obstruction, the most common cause of which is duodenal ulcer. If, in addition to the gastric retention, there is typical gastric hyperperistalsis, the presence of a duodenal ulcer is well-nigh certain. In short, we consider the combination of these two signs as being quite as diagnostic as any other evidence that can be obtained, not even excepting bulbar deformity. Dilatation of the antrum, while simply one of the later manifestations of obstruction in the vicinity of the pylorus, should at least arouse suspicion of obstructive duodenal ulcer, since this is a frequent cause.

Spastic manifestations in the stomach, such as migratory in-

cisura or a temporary hour-glass, are merely indicative of an irritable focus which may or may not be an ulcer in the duodenum (Fig. 87).

The value of these indirect signs depends considerably upon their frankness, their combinations with each other, and their concordance with the general aspects of the case. Hyperperistalsis,



Fig. 87.—(134,500.) Hyperperistalsis. Six-hour retention. Diagnosis duodenal ulcer.

of a pronounced and characteristic type, is alone worth perhaps 60 per cent. for diagnosis. Backed by a good clinical history, it has still greater value, but there remains a small number of cases in which this combination results from disease of the gall-bladder or appendix, so that it is more conservative to carry out the serial examination in addition. There is always this to be said of indirect

signs, that where they fall short of establishing a diagnosis, they contribute to diagnostic certainty, or, at all events, guide the observer in the right line of inquiry.

At the risk of being tedious I wish to reemphasize a point I have often mentioned, namely, that the examiner should be acquainted with the history and clinical data in every case. With this knowledge he is enabled to direct particular attention to the most probable seat of trouble; his opinion is, as it should be, tempered by all the facts, and he is less likely to err in his conclusions. I would not be understood as saying that the roentgenologist should base any diagnosis on the history only, or even chiefly. The clinician can do that. Nor do I mean that a contradicting history should swerve the roentgenologist when his own evidence is conclusive. We all recognize the fact that the history of duodenal ulcer is not always typical. We know, further, that the typical symptoms of duodenal ulcer are sometimes exactly imitated by those of a chronic appendicitis or cholecystitis. But the anamnesis and clinical data in most instances are more or less directive and eliminative. They may often assist in differentiating between bulbar deformity produced by the adhesions of a pericholecystitis and by duodenal ulcer. A correlation of all the findings is advisable, as a rule. In short, I believe that no diagnosis can be too strongly fortified, and that any gross discordance between the findings from all sources should make the examiner cautious in his opinions. As a corollary of this, I believe that we should not pin our exclusive faith to any single method of examination. Rather, I think, should we make use of every technic that offers help, and weigh the results as a whole.

CHRONIC DUODENAL ULCER *

WILLIAM J. MAYO

In the presidential address delivered before the American Surgical Association in 1900, Dr. Robert F. Weir¹ called attention to the surgical possibilities of ulcer in the duodenum. In his masterly presentation of the subject he dealt chiefly with the acute cases, especially those in which perforation had taken place. Within the following year the condition was recognized in examining patients in our clinic and several patients were operated on. The previous history in each case was so distinctive as to attract attention at once. Before the perforation occurred the patients suffered from intermittent digestive disturbances, followed by intervals, sometimes of great length, in which they were fairly well. The symptoms complained of were characteristic—hyperacidity, hypersecretion, hunger pain, food relief, and, in the later stages, the phenomena which accompany obstruction.

These various findings were most interesting, and led promptly to a more careful examination in similar cases in which we had been operating for so-called pyloric obstruction, supposedly due to ulcers of gastric origin. The investigation showed that a high percentage of the ulcers believed to be pyloric were in reality in the first portion of the duodenum.

In 1904 I reported to the American Surgical Association 58 cases of undoubted duodenal ulcer in which C. H. Mayo and I operated.² Even at that time we had no conception of the frequency with which duodenal ulcer had occurred. This is shown by a comparison of the statistics of cases in which operation was done in our

* Read before the Association of American Physicians, May 11, 1915, Washington, D. C. Reprinted from Jour. Amer. Med. Assoc., 1915, Lxiv, 2036-2040

clinic, as noted at subsequent dates: In 1904 the relation of gastric ulcer to ulcer of the duodenum was: gastric, 73 per cent.; duodenal, 27 per cent.; in 1907, gastric, 52 per cent.; duodenal, 48 per cent.;

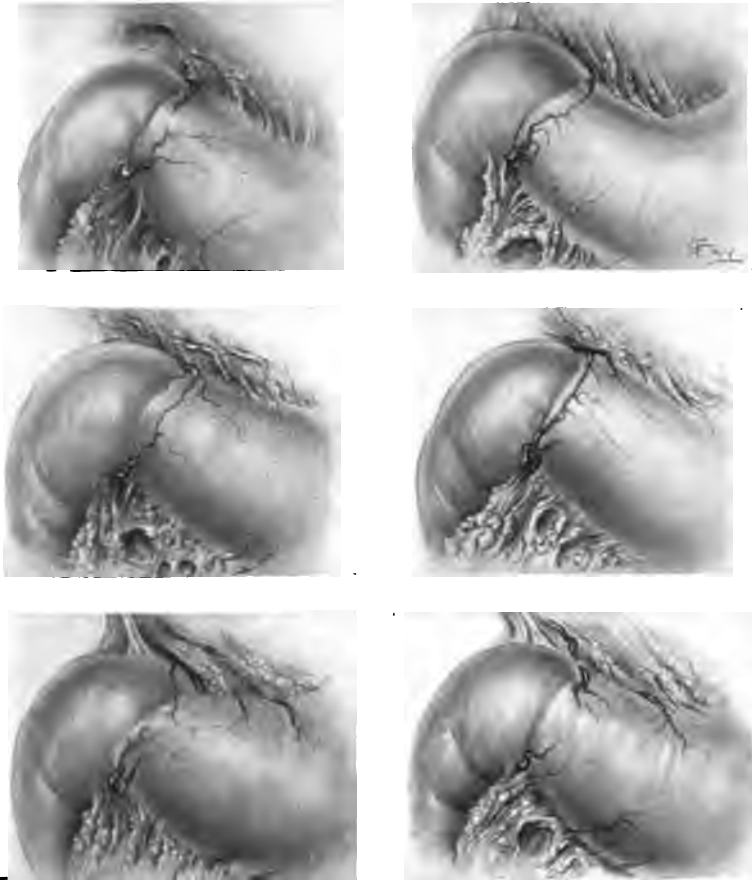


Fig. 88.—Types of pyloric vessels in relation to the location of the pylorus.

in 1910, gastric, 35 per cent.; duodenal, 65 per cent.; in 1914, gastric, 27 per cent.; duodenal, 73 per cent.

Our work during this early period was greatly stimulated by the splendid contributions of Robson and Moynihan, whose observa-

tions and results agreed with those in our clinic. The fact that surgeons working simultaneously in different countries should come to the same conclusion seemed very significant.

The idea that duodenal ulcer was more frequent than gastric ulcer was slowly evolved. Surgeons investigating conditions at the operating table were more readily convinced than physicians working along the lines of specialized gastro-enterology. A prominent specialist in gastro-intestinal diseases once asked, "How is it possible that you, a general surgeon, see so many of these cases while I, who am devoting all my time to this work, see so few?" I could only answer, "The thickness of the abdominal wall prevents you from seeing them."

Postmortem statistics have been and are still quoted in opposition to the view that duodenal ulcer is a frequent condition. For example, the statistics of Rokitansky,³ master pathologist, were published in 1839. Brinton,⁴ whose statistics are so readily quoted on every occasion, published his work in 1857. These did not represent Brinton's personal observations, but what he had gleaned from postmortem records obtained from diverse sources previous to that time and did not necessarily represent facts, but their interpretation in the light of the time when the statistics were compiled. The statistical method of settling such questions is none too good at best, and when the statistics are from fifty to seventy-five years old, they can hardly be accepted as representing modern thought on the subject of gastric and duodenal ulcers.

The methods of clinical study have been even more chaotic. For example, compare the clinical diagnoses of gastric ulcer on admission to the hospital with the necropsy findings ten years ago. Take three hospitals in Philadelphia: University Hospital, clinical diagnosis of gastric ulcer, 0.48 per cent.; Pennsylvania Hospital, clinical diagnosis, 0.13 per cent.; Blockley Hospital, as the result of necropsy findings, giving 1.42 per cent. of gastric ulcer (Francine⁵). In other words, in two hospitals of exactly the same character in the same city ulcer was diagnosed clinically nearly four times as often as in the other, while both fall short of the actual postmortem findings in the third hospital from three to eleven times.

Duodenal ulcer was seldom mentioned as a clinical or necropsy finding. Francine says: "We cannot base accurate or conservative conclusions on data obtained from clinical observation."

Without going further into the question of the relative frequency of gastric and duodenal ulcers, it may easily be seen that the

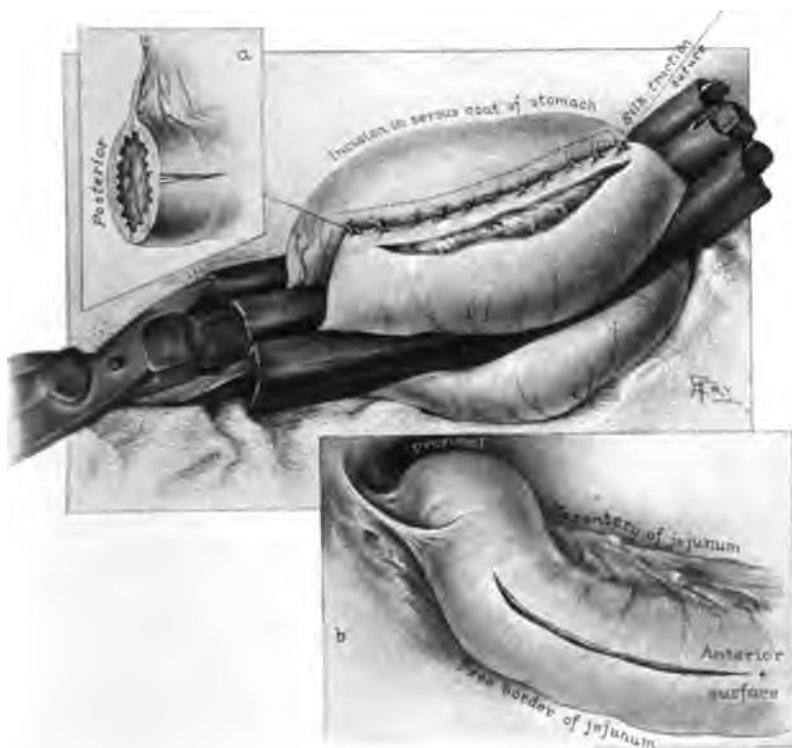


Fig. 89.—Interrupted seromuscular sutures, posterior row, in place. Peritoneal and muscular coats of jejunum incised to mucosa. Dotted line on stomach indicates line of incision. *a*, Line of incision in jejunum, not opposite mesentery, but on the upper left side; *b*, line of incision in jejunum.

clinical and postmortem demonstration of peptic ulcers has been, to say the least, misleading. The Germans, who were slow to investigate duodenal ulcer, were the greatest comfort to those who did not believe that duodenal ulcer occurred with any degree of frequency. A celebrated German surgeon said in explanation: "We relied too much on the supposed knowledge of the gastro-

intestinal specialist; he was so positive that we really thought he knew." The change in opinion in Germany within the last two years has been very remarkable, and is best demonstrated by Kümmell's⁶ statistics of the Eppendorf Hospital. Quoting from his recent paper: "It is not uninteresting for me to explain to you how in the relatively short time, especially within the last few years, the number of duodenal ulcers has increased among us, and how a notable gain in the *actual objective material* in our *pathologic institutes* has been brought to light by Fränkel."

RELATIVE NUMBER OF GASTRIC AND DUODENAL ULCERS
(KÜMMELL)

From 1897 to end of 1911.	191 gastric ulcers to 16 duodenal
1912.	10 gastric ulcers to 7 duodenal
1913.	11 gastric ulcers to 30 duodenal
First three months, 1914.	no gastric ulcers to 12 duodenal

Of equal significance is the work of Schrijver,⁷ of Amsterdam, who shows the same striking increase in the recognition of duodenal ulcer. Those experiences can be multiplied from all the advanced European clinics. The clinical frequency of duodenal ulcer has been demonstrated by exact methods under the sense of sight in the operating-room.

Wilkie,⁸ of the Royal Infirmary of Edinburgh, has found 41 (9.9 per cent.) duodenal ulcers in 490 postmortems. In only 6 cases had antemortem diagnoses been made; in these operations had been done. Wilkie quotes Gruber that 75 per cent. of duodenal ulcers found after death had not been diagnosed during life.

The experimental production of gastric and duodenal ulcers as yet appears to have little bearing on chronic callous ulcer. There is a type of acute ulcer, probably toxic in origin, which gives rise to sudden severe symptoms, often followed by perforation or hemorrhage. These patients, left untreated, either die or completely recover within a few weeks. The ulcers are multiple; there is no callus, and several ulcers may perforate simultaneously. So far as I have been able to observe, experimental ulcers belong to this class and are of very little value in determining the character and position of the chronic callous ulcer of the duodenum. The latter are

usually single, seldom begin with an acute attack, and as a rule the earlier symptoms are less severe than the later ones.

It is interesting to speculate as to what diagnoses were made in the cases of duodenal ulcer prior to our present knowledge. It is altogether probable that a large percentage of chronic duodenal ulcers were not diagnosed at all. Some were believed to be gastric

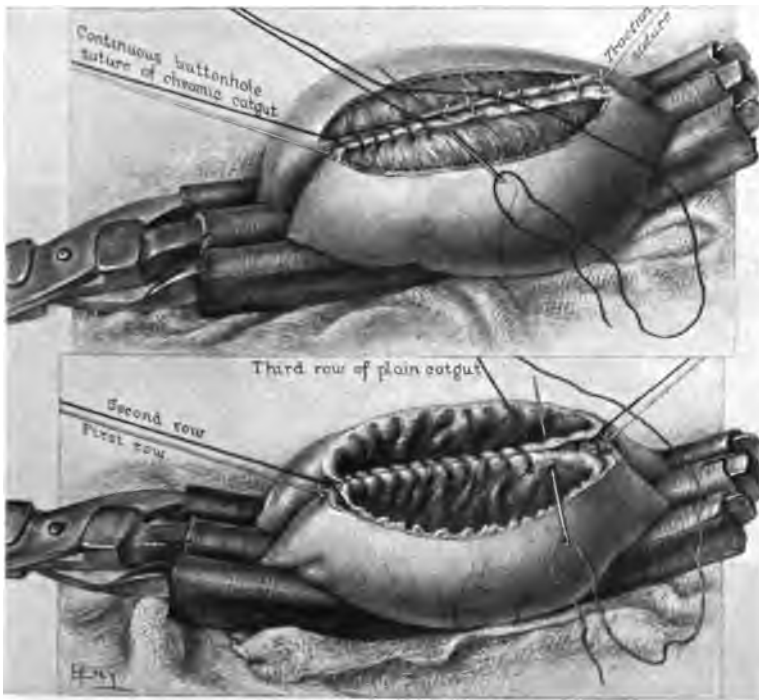


Fig. 90.—Upper figure shows through-and-through catgut suture of posterior wall before opening the mucosa. Dotted line shows where mucosa is divided. Lower figure shows mucosa flaps stitched across with catgut suture.

ulcers. A high percentage of acute perforations were believed to be acute appendicitis, since the fluids quickly gravitate into the right iliac fossa, and the appendix as well as the surface of the intestine early shows marked evidences of peritonitis. Ten years ago it was taught that an appendix, apparently normal in its mucosa, under certain conditions permitted bacteria to pass into the peritoneal

cavity, causing septic peritonitis. The mistake was often not discovered, even at operation, and the death of the patient came after extensive peritoneal involvement had obscured the site of perforation in the duodenum sufficiently to prevent recognition. The experience of the Massachusetts General Hospital as reported by Codman⁹ is instructive in this respect.

I shall not go into the question of the etiology of duodenal ulcer. It is quite evident that the same causes which produce gastric ulcer produce duodenal ulcer. The thrombosis and embolism theory, the nerve theory, the bacterial theory, the mechanical theory, and the erosion theory all have their advocates. The latest recruit to the infection theory is Rosenow,¹⁰ whose splendid investigation as to the relation of the streptococci in the terminal capillaries of the mucosa to ulcer of the stomach and duodenum is most illuminating. This theory is borne out by the edematous inflammatory character of the ulcerous duodenum found when operating during an exacerbation of the symptoms, and further by the fact that following acute perforation of an ulcer, if the patient is so fortunate as to recover, the ulcer heals as though some harmful agent had been extruded. If later other symptoms are manifested, they are due to the obstruction or deformity which follows in the wake of ulcer.

One possible source of injury to the mucosa of the lesser curvature of the stomach and duodenum which may have some bearing on the etiology of peptic ulcer, and also to cancer of the stomach, is hot drinks. Solid food is masticated in the mouth, and then passes into the fundus of the stomach, where it is retained during the early period of gastric digestion. If the food is very hot, it is more or less cooled in the act of mastication, but drinks are taken into the stomach much hotter than can be borne in the mouth. Any one taking the trouble to experiment will probably find they have been in the habit of swallowing fluids much too hot to be held in the mouth comfortably. The stomach and duodenum give little immediate indication that the fluid is too hot. These hot fluids are carried rapidly along the lesser curvature into the duodenum to the exact situation in which the majority of ulcers are found, possibly removing the protective mucus which prevents autodigestion and

which may result in chronic irritation. Extremely cold drinks may have the same effect. Primitive men and animals do not take their drinks hot and, so far as we know, seldom have gastric cancer.

The experiments of Jefferson¹¹ as to the *canalis gastricus* have shown that liquids, when taken in considerable quantity, pass rapidly along the lesser curvature and into the duodenum without mixing with the food-mass in the fundus.

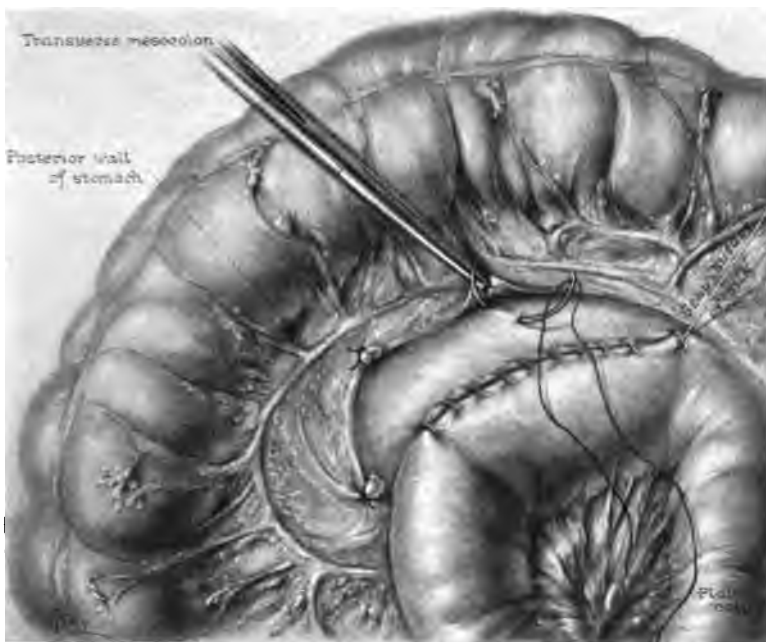


Fig. 91.—Stay suture distal to the anastomosis and suture of margin of the opening in mesocolon to stomach. Note that stomach hangs below transverse mesocolon, making a funnel.

The pyloric veins are most valuable in differentiating gastric from duodenal ulcer. A short, stumpy vein comes out from above, and another from below, the pylorus, sometimes sending a small branch across the top of the pylorus (Fig. 88). These veins are quite unlike the vessels of other situations of the stomach, and when their peculiarities have once caught the eye, they serve readily to

locate the pyloric ring. Gastric ulcer in the pyloric end of the stomach is not often mistaken for duodenal ulcer, but for cancer, as in this situation a tumor usually forms in connection with the ulcer as the result of muscular hypertrophy and edema.

The larger number of ulcers of the duodenum are located in the first $1\frac{1}{2}$ inches, more often on the anterior wall. A number begin just below the pylorus, and at first glance they appear to involve the pyloric ring, especially when extensive and obstructive, but careful examination will show that they are duodenal. The deeper, larger ulcers and those which bleed excessively are more often situated on the posterior wall, the callus sometimes extending into the head of the pancreas. Such ulcers may be concealed from view underneath the pyloric ring, but seldom involve the gastric mucosa. When an ulcer is situated on the posterior wall, a superficial contact ulcer will usually be found opposite on the anterior wall. The mucosa of the duodenum is thin, smooth, and granular, and chronic duodenal ulcers may not therefore have the characteristics we have learned to expect from experience with gastric ulcers. I have excised a number of duodenal ulcers in which there was considerable scar tissue in the submucosa and muscularis and marked evidence of localized peritonitis; yet the actual ulcer was a mere slit or dimple surrounded by an eroded, discolored, "moth-eaten" patch of mucosa. This is the type of ulcer which occurs on the anterior wall unless there is a corn-like thickening over the top of the ulcer, in which case it will have the size, depth, and callus characteristic of gastric ulcer.

Ulcers may exist in the duodenum at any point above the opening of the common duct or even down as low as the opening. I have observed three cases marked by repeated hemorrhage in which the ulcer involved the papillæ of the common duct on its superior surface.

A high percentage of duodenal ulcers perforate the mucosa and muscularis to the peritoneal coat. These are classified as chronic perforations; complete perforation having been prevented by thickening of the peritoneum or adhesions to the gall-bladder, omenta, suspensory ligament of the liver, etc. Many times an

acute perforation actually takes place with the recovery of the patient, since the opening may be small, allowing but little fluid to escape and that fairly sterile. In such cases patients have a localized peritonitis with extreme pain lasting for several days and then make a spontaneous recovery. I have explored a number of such cases during an attack of acute localized peritonitis and have discovered the duodenal opening which had been spontaneously closed by adhesions. Occasionally absorption of the escaping products is incomplete, and a phlegmon forms, usually underneath the liver, which can be opened and drained. If this is done gently, the original source of leakage in the duodenum will probably not be reopened.

The symptomatology of duodenal ulcer is so well known that in the typical cases failure of diagnosis should not occur. The hunger pain and food relief, hyperacidity and hypersecretion, and, in the later stage, obstructive phenomena, leave little doubt as to the character of the lesion. Failure in differential diagnosis may be due to accompanying diseases of the gall-bladder, appendix, etc., which occur in about 16 per cent. In our experience, actual hemorrhage takes place in somewhat less than 25 per cent. of the cases, but if one is satisfied to ask the patient questions and accept doubtful evidence as to black stools, etc., this percentage can be increased to as much as 70 per cent. We have not found occult blood a reliable symptom and do not attach a great deal of importance to it. I say this with some reluctance, since many diagnosticians for whom I have the highest respect believe that it is a diagnostic sign of very great importance.

The roentgen ray is a very important and increasingly valuable means of diagnosis. When taken in conjunction with the clinical history, a diagnosis can be made in approximately 95 per cent. of cases.

The physical examination, including the use of the stomach-tube, is important as evidencing hypersecretion and food retention, tumor, visible peristalsis, etc. Laboratory diagnosis, that is, microscopic and chemical examination of gastric contents, has some value, but is largely of a corroborative nature and has been very greatly overestimated. Dividing into four groups the means of

diagnosis, the history is of first importance, the roentgen ray second, the physical examinations (stomach-tube findings, etc.) third, and the purely laboratory findings a poor fourth.

One of the most curious phenomena connected with duodenal ulcer is its intermittency. The disease usually begins in young males (83 males to 17 females); after a period of some weeks of symptoms there is a cessation, more or less complete, and the patient goes for months without any knowledge of his ailment. Then the symptoms recur and after a time the usual remission takes place. This may go on for years until finally obstruction supervenes and the symptoms become more or less constant, although the gastric muscles may, by hypertrophy, become competent to overcome considerable obstruction, in this respect acting quite like the heart in valvular disease—periods of competency followed by periods of incompetency.

A study of the history of the natural course of chronic duodenal ulcer makes the prospects of permanent cure by medical means open to question. I have seen a number of so-called "medical cures" and have not been able to determine that there was any material difference between them and the spontaneous remissions. The ulcer, as far as roentgen-ray evidence is concerned, shows no physical change in the period of improvement. In operating during this period, no sign of healing is found. By means of alkalis, restricted diet, frequent feeding, largely milk and cream, whereby chemical corrosions are controlled, patients with chronic duodenal ulcers are relieved; a remission of the symptoms being secured and maintained for an indefinite length of time. But such patients cannot be looked on as cured unless they can go back, without a recurrence of trouble, to the regular diet of the grade and character obtainable by the average man. As a matter of fact, relapse usually takes place under such circumstances, and the dangers of perforation and hemorrhage are ever present.

Other things being equal, after failure of reasonable medical treatment, patients with unhealed chronic duodenal ulcer should be considered surgically. To evade operation in the unhealed case is, I believe, a risk not commensurate with the value received from

operative interference. No class of patients gives better results following surgical intervention.

A recurrence of symptoms after operation is most often due to defective surgical technic, usually a gastrojejunal stitch ulcer occurs, caused by the use of continuous silk or linen threads. Such sutures may hang, causing ulceration and trouble for months or years. The stitch ulcer produces the same symptoms as the original ulcer: hunger-pain, food-relief, hypersecretion, and hyperacidity. I have reason to believe that many of the poor results following gastro-enterostomy are the sequelæ of sutures which have finally passed out.

The clinical course of stitch ulcers is quite typical. The patient is operated on for chronic duodenal ulcer and gastro-enterostomy is done. He is relieved, and for from three to six months feels fairly well; he then begins to develop the former symptoms and it is supposed that the original ulcer has recurred. In the course of some weeks or months, about the time the suture finally separates, gradual improvement takes place.

Recently a large number of articles have appeared dealing with the necessity of closure of the pylorus to prevent food from passing down into the ulcerated area. The evidence as to the necessity of this procedure is not clear. Stitch ulcers and improperly selected patients are responsible for the recurrence of the symptoms in most instances. We have not found that the patients in whom the pylorus was blocked have in any way had results superior to those in whom it was not blocked following simple gastro-enterostomy. If perforation is impending, I think it wise to block the pylorus and cover the ulcer; if there have been hemorrhages, this should be done and the vessels in the vicinity of the ulcer carefully tied. But there is no evidence that the routine blockage of the pylorus is advisable or necessary, and if it cannot be done without additional risk, I think perhaps it had better be left undone.

The enthusiastic operator who has made gastro-enterostomies because of symptoms or of supposititious ulcers which he believed he could see or feel, has greatly harmed gastric and duodenal surgery. In our clinic more than 100 unnecessary gastro-enterostomies have been cut off because of secondary complications, such as

chronic bile regurgitation, etc. Fourteen of these were our own patients operated on in the early period, when it was not understood that a patient should not be operated on unless the ulcer could be actually demonstrated. At the time of these secondary operations careful search did not reveal evidence that ulcer of the stomach or duodenum had ever existed. Now that blockage of the pylorus has become popular, an alibi is established in advance inasmuch as the scar made by the ultimate passage of the suture into the gastro-intestinal lumen creates a reasonable doubt as to whether the scar is due to the healed ulcer or to the thread. In other words, pyloric blockage often establishes false testimony.

In the large majority of cases gastro-enterostomy is the ideal operation for duodenal ulcer, with or without infolding the ulcer (Figs. 89, 90, and 91). In selected cases, excision of the ulcer in conjunction with the gastroduodenostomy of Finney is the operation of choice. In those rare cases in which true jejunal ulcer forms following gastro-enterostomy, the jejunal ulcer should be excised, the stomach and jejunal openings closed, and the Finney operation done after cutting off the gastro-enterostomy. Following surgical intervention, the patient should be under good medical advice until permanent cure is assured.

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ROENTGEN OBSERVATION OF THE GALL-BLADDER AND HEPATIC DUCTS AFTER PERFORATION INTO THE DUODENUM *

RUSSELL D. CARMAN

The roentgenologic demonstration of a barium-filled gall-bladder in a living patient is sufficiently unusual to warrant its report. So far as I am aware, no similar case confirmed by operation or necropsy has appeared in the roentgen literature.

The patient, a woman aged fifty-four, had had a cholecystostomy for gall-stones in January of this year, elsewhere. She came to the Mayo Clinic May 22d. In the scar of the operation wound were two sinuses discharging pus, and surrounded by a movable, nodular mass. The total acidity was 4, all combined; no food remnants. Hemoglobin, 80 per cent. The clinical symptoms consisted chiefly of some hunger distress, belching, and watery regurgitation.

At the roentgen examination no retention from the six-hour meal was found. When the stomach was filled with the second meal, the pyloric end showed a smooth, concentric filling defect, giving the lumen a conical form, and typical of scirrhus carcinoma. Far up in the right abdominal quadrant was a dense collection of barium with sprig-like branches (Fig. 92). From its situation this was believed to be in the gall-bladder, indicating a communication between it and the upper intestinal tract, which was reported to the clinicians in charge of the case. The tendril-like branches were deemed to be due to the extension of barium into the hepatic ducts.

At operation (E. H. Beckman, June 28, 1915) the external sinuses were found to lead into a dense carcinomatous mass sur-

* Reprinted from Jour. Amer. Med. Assoc., 1915, lxx, 1812.

rounding the gall-bladder and involving the stomach. By reason of its extent the cancer was not exsectable. The gall-bladder itself, which was excised, simply showed a chronic cholecystitis with particles of barium adherent to the mucosa. The fundus of the gall-bladder communicated with the duodenum through a perforation.

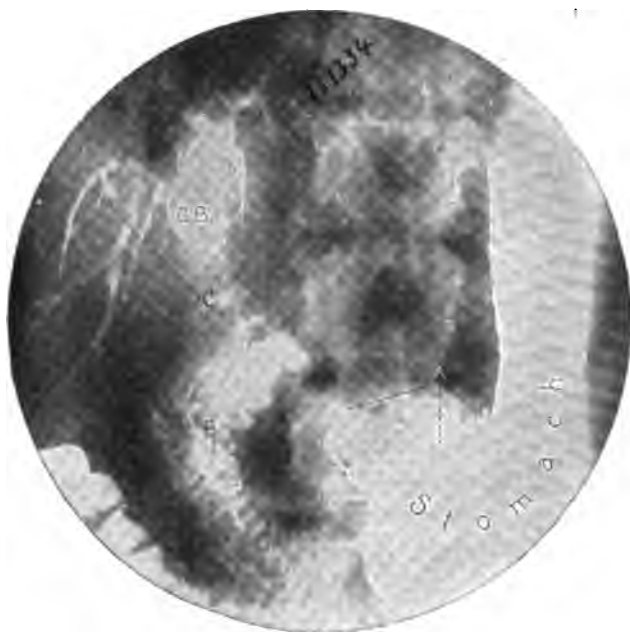


Fig. 92.—Roentgenogram: A, Carcinoma, pyloric end of stomach; B, duodenum; G. B., barium in gall-bladder; C, barium in hepatic ducts.

At necropsy on the following day the perforation, which had been covered by the surgeon as well as possible, was found in the anterior wall of the first portion of the duodenum, toward the former site of the gall-bladder. Metastases were noted in the liver. Some barium was seen in the hepatic ducts.

PAPILLOMAS OF THE GALL-BLADDER *

CHARLES H. MAYO

Few new operations on the gall-bladder have been developed recently. Very early in the surgery of gall-stones cholecystotomy, cholecystostomy, and cholecystectomy were common procedures, some surgeons advocating one and some another.

Later, exploration of the ducts, especially in cases in which jaundice was or had been a factor, was practised by some surgeons, who reported an unusually large percentage of cases of common-duct disease, as primary instead of secondary surgical procedures. Such examinations also disclosed pancreatitis of some form as an occasional complication. Pancreatitis had been considered a rare disease by those who did not explore and whose knowledge was derived from autopsy reports. Such explorations at the operating-table led to the cure of a larger percentage of cases, many patients being saved time and dangers of a second operation. The same can be said of examinations of the appendix for associated disease at operations on the stomach and duodenum for ulcer.

In an early day surgeons were often chagrined in operating for gall-stones to find no evidence of stone, but an apparently healthy gall-bladder. In these cases general exploration was forced upon them, and thus the advantage of always exploring, when not contraindicated, became an accepted routine of abdominal operations. Cholecystitis associated with stone formation was commonly noted. Thick-wall gall-bladders without stones, but giving symptoms of cholecystitis, were next drained or removed. Stones were occasionally found in thin-wall and blue gall-bladders, which, when

* Read before the American Surgical Association, June 10, 1915. Reprinted from *Annals of Surgery*, 1915, lxii, 193-197.

free from adhesions, formerly had been considered free from disease. Some such gall-bladders, upon cholecystostomy, showed the peculiar markings of "strawberry" mucosa (Fig. 93). It was then appreciated that disease of the mucosa could exist in a gall-bladder which, from its external appearance, was apparently healthy. In cases in which well-marked symptoms of gall-bladder disease existed the gall-bladder was opened, examined, and drained, or removed according to the personal judgment of the operator after he had proved to his satisfaction that the symptoms were not

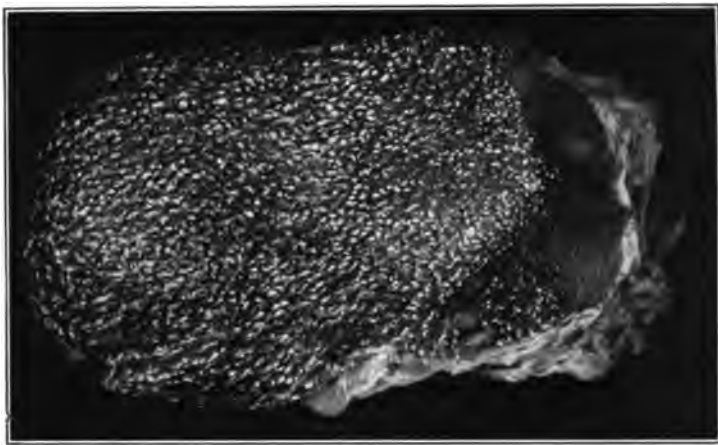


Fig. 93.—(132,852.) Strawberry gall-bladder.

caused by other abdominal conditions. Such gall-bladders were described as "catarrhal," a term which always leads one to think of an excessive mucous secretion or of mucosa with a diseased surface, but which really means inflammation at the base of the cells involved.

If an inflammation is from bacterial infection, the lymphatics draining the diseased area are enlarged and soft in acute processes and harder in chronic processes, from exerting their protective function against acute general involvement by absorption. Lymphatic glands are always located at the neck of an organ in movable tissues adjacent to the vascular supply. There are two or three

glands on the cystic duct and several along the hepatic and common ducts; the latter drain the head of the pancreas and the duodenum. Inflammation of the pancreas, however, usually involves also the gall-bladder or ducts. Ulceration of the duodenum may cause swelling of these glands. If the symptoms of gall-bladder disease indicate exploration, and upon examination there are no gall-stones and but little change in the appearance of the gall-bladder, these glands should be palpated. Given sufficient symptoms for surgical intervention, if these glands are swollen without other adequate cause, as from diseased duodenum, pancreas, or general abdominal infection, the gall-bladder should be removed



Fig. 94.—(A106,500.) Papillomas.

whether or not stones are present. On the other hand, given such symptoms, if no gall-stones are found and if the glands are not swollen, then some other cause for the symptoms must be searched for, since the patient probably will not be relieved by an operation on the gall-bladder.

What causes inflammation of the gall-bladder? There are several theories: First, that of an ascending infection from the duodenum by way of the ducts; second, infection by way of the lymphatics; and third, infection by the portal route through the liver which fails to destroy the bacteria brought to it. The first theory has not been generally accepted. The second has been accepted with considerable reservation for some conditions. The third has been more generally accepted. The first and last theories, however, acknowledge that living bacteria in the bile penetrate a

living healthy mucosa lining the gall-bladder which is made for, and should be able to, protect itself against such conditions. To believe this we must consider the surface of the mucosa as the vulnerable point, which is possible but less probable than that the attack is commonly in the unprotected rear, that it is by way of the blood-stream.

The vascular route, as suggested by Rosenow, looks very plausible. We have long accepted the fact that the well-known in-



Fig. 95.—(A78,934.) Papillomas and strawberry gall-bladder.

fectious diseases have each a specific bacterium which causes, according to the type, a definite group of symptoms in lungs, intestines, skin, mucous membranes, tonsils, or elsewhere. To Rosenow is due the credit for the theory that the bacteria which cause similar acute and chronic diseases, such as cholecystitis, have the same definite function, and that when they enter the blood-stream they search out locations with the same environment as that in which

they originated. He has shown that changes in environment can change bacteria in appearance, and in the effects caused by them, and in their tendency to locate in vascular or mucous surfaces, or to cause inflammation of the joints. Such bacteria are cultured in a certain focus in the body, and thence through the vascular system, producing a varying degree of infection in the gall-bladder, while bacteria cultivated from acute gall-bladder inflammation entering the vascular system may produce similar acute gall-



Fig. 96.—(96,944.) Chronic cholecystitis, strawberry gall-bladder with papilloma.

bladder inflammation in another person. In certain investigations, some of which were made at our clinic, Rosenow has shown that bacteria cultivated from the tissues of the gall-bladder and those from the glands along the ducts showed similar growth; further, that such cultures of bacteria injected into dogs caused similar changes in their gall-bladders. Such a result occurred approximately in two-thirds of the experiments. Not alone, however, is the gall-bladder affected. Some experimental animals

show associated rheumatism and some heart, kidney, or other involvement, due to bacterial changes from new environment.

Cholecystitis then is a disease of the gall-bladder caused by bacterial invasion of the wall of the structure. In this direct manner there are changes in its circulation, with edema, infiltration, exudation, swelling of the lymphatic glands, and local necrosis of the mucous membrane; for example, strawberry gall-bladder. This infiltration of the gall-bladder structure with cells and bacteria prevents the distention and contraction of the sac and causes pain. Thus may be caused qualitative food dyspepsia and symptoms of epigastric gas pressure.

Papillomas of the gall-bladder occur in the same manner, but instead of a primary destructive effect, there occurs locally a hyperplasia or overgrowth which later may become necrotic. That the disease is more common than is ordinarily supposed is indicated by the fact that it was found 107 times in 2538 cases of cholecystectomy performed in our clinic from January 1, 1907, to June 1, 1915. The glands above described were enlarged in these cases. The pathology has recently been studied by MacCarty and Irwin, who summarize the results of their observations as follows:

1. Acute catarrhal cholecystitis.
2. Chronic catarrhal cholecystitis.
3. Papillomatous catarrhal cholecystitis.
4. Malignant papillomatous cholecystitis.
5. Carcinomatous catarrhal cholecystitis.
6. Chronic cholecystitis.
7. Chronic cystic cholecystitis.
8. Purulent necrotic cholecystitis.

Of these groups, 3 and 4 have been the subject of the present study. In all the cases in group 3 (Figs. 94 and 95, papillomatous catarrhal cholecystitis, the mucosa is intact. The papillomas vary from two to five or six times the length of normal villi. They are generally pedunculated, racemose, and usually white or yellow. They appear in any portion of the organ, being confined neither to the neck nor the fundus. Microscopically, they appear to be hypertrophic villi, the tissue elements of which present a hyperplastic condition. The connective and

glandular tissue are greatly increased, the latter being so distorted that sections cut the glands in many different planes. The epithelium of the glands is hypertrophic and occasionally hyperplastic, and practically always completely covers the growth. In the stroma one often finds large round or oval cells which contain fat or some fatty substance, this condition probably being responsible for the yellowish, gross appearance of the growths.

In no case are there any early signs of carcinoma, although similar hypertrophic conditions of the villi have been seen in association with carcinomatous outgrowths of the gall-bladder. The condition occurs in acute catarrhal cholecystitis, chronic catarrhal cholecystitis, cystic catarrhal cholecystitis, carcinomatous catarrhal cholecystitis, and purulent necrotic catarrhal cholecystitis. It occurs with and without the association of stones, and is more frequent in females than in males, probably due to the fact that more gall-bladders are removed from females.

Papillomas are but an associate pathologic condition found in cholecystitis. One theory of origin is that they possibly originate in surface cracks through overdilatation, caused by mucous obstruction and swelling of the mucosa incident to cholecystitis associated with the presence of bacteria or irritants from stagnation of gall-bladder contents. It is, however, not so plausible as Rosenow's theory of vascular-borne infection of the gall-bladder mucosa.

Like papillomas in other portions of the body, those in the gall-bladder undergo an irregular or perverted epithelial hyperplasia which manifests itself in marked reduplication of the rows of epithelial cells. This condition constitutes malignant papillomatous cholecystitis. Differentiation between this condition and carcinomatous catarrhal cholecystitis must be made with reserve because it is possible that the one is but a stage of the other.

From the surgical standpoint, it is important to note that the papillomas of the gall-bladder are not cured by temporary drainage, but that cholecystectomy should be performed.

CHOLECYSTOSTOMY VERSUS CHOLECYSTECTOMY *

CHARLES H. MAYO

After the many years in which operations have been done on the gall-bladder and ducts, it would seem that our knowledge of the pathologic conditions, the indications for medical treatment or for surgery would be quite settled. Medical treatment, though apparently fairly successful in cholecystitis, which has a periodic recurrence of symptoms, yet has often led to delay and later operations for secondary complications. Instead of general progress in surgery, secondary operations for diseases of the gall-bladder and ducts have become so frequent as to be a subject of comment, and many who suffer from such diseases delay operation knowing that, while the percentages of cures are high, there are failures and other operations may be necessary.

An investigation of the 370 cases of diseases of gall-bladder and ducts coming to operation in our clinic during four months, from July to November inclusive (1915), showed that 48 (13 per cent.) patients had already been operated on for these various conditions. It was also noted that the majority being women, naturally there had been many previous operations, such as removal of the appendix, of the right ovary, and fixation of the right kidney.

Nevertheless, considered all in all, gall-bladder surgery has made great progress during the past twenty-five years. Culled, as most of the cases were in the early period, from diseases of the stomach, it is found that the condition is a common cause of reflex irritation, vying with the appendix in creating gastric symptoms.

* Read before the Southern Surgical and Gynecological Society, Cincinnati, Ohio, December 15, 1915. Reprinted from the Transactions, 1915.

Early in this period the operations cholecystotomy, cholecystostomy, cholecystectomy, and drainage of the ducts were developed. Too often only advanced cases were diagnosed, and secondary complications of infective disease of the ducts and pancreas led to a high mortality. Thus the surgery of this region suffered for a time from a vicious circle; late operation and complications gave a high mortality, while the high mortality led to delay. Through improved technic and a study by sight of the progress of the disease in the living, the operation, usually cholecystostomy, became a safe procedure and resulted in a large percentage of cured patients, with many others improved.

After a safe technic had been developed, the number of cholecystectomies as compared to cholecystostomies increased for a time, amounting to one-third of the operations performed. Later a great effort was made to save the gall-bladder, and nearly 80 per cent. were preserved. With growing knowledge of the subject, and influenced by a recurrence of symptoms which showed many failures to cure, cholecystectomy became the rule, and now nearly 90 per cent. of diseases of the gall-bladder are so treated, only some special circumstance of infection, perforation, great age, or general condition leading to the choice of cholecystostomy. Should further symptoms develop, cholecystectomy is advised as a later procedure.

It is hardly fair to base our judgment as to the present state of surgery on reports including the relative value of results in cholecystectomy or cholecystostomy, which were made during the imperfect and developing period of the early surgery of these diseases, say, ten to twenty years ago, or including a proportionately large series of unproved medical cases so diagnosed. Knowledge of the subject has progressed so far that the diagnostician prides himself in stating that the disease is cholecystitis with gall-stones, or cholecystitis without stones, common-duct stone, cholecystitis with secondary pancreatitis, cystic gall-bladder, or empyema of the gall-bladder, perforating gall-bladder, or cholecystitis with gastric syndrome. Previously the gall-stone was the entity: now it and the other conditions are all secondary to cholecystitis, which

may be acute, chronic, or quiescent. When formerly a vague idea of infection was conceded, this was generally believed to be of a so-called catarrhal type, whatever that may have meant to the mind of the user of the term. As to the origin of the supposed surface infection of the mucosæ, there has been much discussion as to whether it arose from an ascending infection through the ducts from the duodenum or by way of the lymph-channels, or that bacteria from the intestine passed by the portal circulation through the liver to be distributed by the bile. These possible facts or fancies have given way to the theory of a rear attack by vascular-borne bacteria to the capillary base of the mucous cells of the gall-bladder, a theory which has been proved by Rosenow in numerous instances. He has shown that the bacteria of local diseases have as selective an affinity for similar environment as have the bacteria of the general and well-known infectious diseases. Of bacteria cultivated from the tissue, not the contents, of diseased gall-bladders taken from man and injected into the veins of animals, with an even chance at all of the body tissues, the effect was to produce cholecystitis in 68 per cent. of 41 animals so treated.

When the etiology of the disease is considered, gall-stones must be relegated to the second place in diseases of the gall-bladder and ducts, and a focus of infections should be searched for.

The diagnosis must be based on the known conditions, which make it possible to recognize cholecystitis as an entity, yet the infective beginning of the disease may be so mild as to be unrecognized until stones develop and mechanical obstruction ensues, or the disease may occur with far graver conditions of infection than occur with stone. The roentgenologic evidence in the diagnosis of such conditions, while often of value, cannot become a factor of great reliability since it recognizes the secondaries of but one group of cases.

Briefly reviewing the anatomy of the gall-bladder, we find that it is an elastic, muscular, distensible sac, attached to the liver, and connected to the common duct at an acute angle by the cystic duct. It is bound to or connected with the hepatic duct in such a manner that when it contracts upon its contents the fluid pressure is the

same in the gall-bladder, cystic and common ducts. The gall-bladder does not completely empty itself like the urinary bladder. It is capable of enlarging its capacity to several times the one to one and a half ounces normally found in it.

Although man has a gall-bladder, there are several animals, including the deer and horse, that have none. It is stated that such animals have somewhat larger ducts, a condition proved clinically to occur in man and in animal after removal of the gall-bladder (Mann).^{*} There are about 30 instances of failure of development of the glands reported in man; also it is often found that certain persons have had cystic, shriveled, or functionless gall-bladders for a long period preceding operation. As to the usefulness of the gall-bladder, some claim it is an unnecessary or obsolete organ, and others that it is a disappearing one. Others claim that the mucus added to the bile from the gall-bladder is of functional importance, and renders the bile less irritating to the ducts of the pancreas should it enter them.

The bile is formed at a rate approximately of an ounce an hour, and delivered through the common duct. This duct does not empty directly into the duodenum, but enters the muscular wall and passes for a short distance between the outer wall and the mucous lining. Any pressure within the bowel thus flattens the duct and prevents regurgitation. Coffey, from much experimental study, states that the mechanical development of this method of entrance is so perfect that the duodenum may burst before any fluid or gas can enter the common duct.

Man is a diverse feeder, eating many things which tend to form gas. This, however, is not serious, as the gall-bladder is capable of symptomless distention to several ounces, and by contraction acts on the delivery of bile as the elastic ureter does on the flow of urine into a full bladder. However, if there is infection of the gall-bladder, he will suffer from so-called gas, with stasis in the duodenum, often associated with pyloric spasm and epigastric fulness or pressure. The gall-bladder, being thick walled in chronic disease, or inflamed with bacteria and infiltration of its wall, can

^{*} Mann, F. C.: In manuscript.

no longer expand and contract without its owner being conscious of the fact. Most patients develop a special or possibly unconsciously selected diet, learning to avoid greases, fried foods, raw apples, etc. They also often have idiosyncrasies to special foods of slow digestion or gas production; the so-called qualitative food dyspepsia, in contradistinction to quantitative food dyspepsia, which occurs following heavy or large meals and gives symptoms one to two hours after eating. These symptoms are induced by interference with peristalsis, or the peristalsis of inflamed areas, and occur with chronic appendicitis with concretions, with Lane's kink, with incarcerated, incomplete hernias, and with adhesions. Some patients complain but little even when gall-stones are present, the original infection having subsided. They suffer less from dyspepsia, as the gall-bladder can expand and contract almost normally. The symptoms then are mechanical, due to obstruction by the stone or to its passage. In some cases, especially cholecystitis, a gastric syndrome with attacks much like those due to gastric or duodenal ulcer occurs. The conditions can usually be differentiated, although we have been unable in some cases to differentiate diseases of the gall-bladder, of the appendix, or duodenal ulcer, since all three of these may exist in the same patient. In duodenal ulcer especially, the roentgen ray is often of great aid. We must occasionally be content with the diagnosis of a lesion with possible reflex symptoms to be proved at exploration if the symptoms warrant the procedure.

It is undoubtedly true that, with reference to gastric symptoms, the crux of the situation is concerned wholly with the question of infection. Gall-stones in gall-bladders free from infection (though it was present when the gall-stones were formed), may give symptoms from obstruction or the movement or passage of the stone, but they do not produce gastric symptoms, or at least such symptoms are not a major complaint. When gastric symptoms are a prominent feature in these cases, infection is the rule, whether stones are present or not, and spells recur followed by free intervals, just as they do in gastric and duodenal ulcer and in appendicitis when they are the result of infection. A large percentage of the

patients who are free from infection may be cured by drainage of the gall-bladder. Because of adhesions and fixation of the gall-bladder and consequent impairment of function due to the operation for drainage, a few of these patients may later be liable to cholecystitis. When infection is lacking, even if there are stones present, the glands along the cystic, common, and hepatic ducts should be found but little enlarged on palpation. Patients in the second or infective group should have the gall-bladder removed at the operation, whether or not stones are present, since the infection is the essential element. In these the glands of the cystic, common, and hepatic ducts should be found enlarged.

For many years we overlooked cases of cholecystitis without stones. Some of these patients had colic and frequent mucus obstructive attacks or local tenderness, yet did not have stones. Often there was a better external appearance of the gall-bladder than in those we were saving after removal of the stones, and the gall-bladder was not even opened upon exploration. Two such patients later developed large stones, as was found several years afterward. Wider experience of the subject led to opening and draining the gall-bladder, and in some cases, if grossly diseased, it was removed, especially the strawberry gall-bladder. Many such patients were relieved while the drainage continued but symptoms recurred when drainage ceased.

Temporary drainage of the gall-bladder in cholecystitis did not give a satisfactory percentage of cures, and as our diagnostic ability improved a gradually increasing number of cholecystectomies were done in cases of infection. The persistence of reflex gastric symptoms after cholecystostomy, if no other cause is manifest, is evidence that the gall-bladder should have been removed.

If cholecystitis is an infection of the wall of the gall-bladder from which bacteria can usually be cultured, then the lymphatic glands draining such an area should show the evidence of such infection. The glands along the common, hepatic, and cystic ducts should be enlarged in such cases, and if not enlarged, some other cause for the symptoms should be searched for. These glands also drain the duodenum and the head of the pancreas, as well as the gall-bladder;

therefore these structures should be examined for ulcer and pancreatic involvement. The latter, however, is often secondary to an infected gall-bladder, and may present a lymphedema, such as is seen in the arm from blocked lymphatic return after removal of the axillary glands following operation for cancer of the breast. The general surgical problem of the present period is the search for the local focus of chronic local infectious processes, and already great progress has been made.

In 2940 cholecystectomies prior to November 1, 1915, we discovered 130 cases of papillary gall-bladder. Papillary growths of other mucous surfaces have a tendency to cancer; their relationship in cancer of the gall-bladder is not known. Approximately 85 per cent. of cancers of the liver are metastatic. Of the 15 per cent. of primary cancer, the great majority are associated with gall-stones and have their origin in the gall-bladder or ducts. Cancer of the gall-bladder in some cases, for example, impacted stone, and possibly in papillary cholecystitis, is undoubtedly avoided by cholecystectomy.

TABLE SHOWING THE RELATIVE MORTALITY OF CHOLECYSTECTOMY AND CHOLECYSTOSTOMY

CHOLECYSTECTOMIES					CHOLECYSTOSTOMIES				
	Total Opera- tions	Cancers	Deaths	Per- centage deaths		Total opera- tions	Cancers	Deaths	Per- centage deaths
1907-1909....	304	..	4	1.3	1085	..	15	1.4	
1910.....	211	2	426	2	7	1.7	
1911.....	100	2	3	3.0	481	2	4	0.8	
1912.....	211	7	4	1.9	427	1	3	0.7	
1913.....	261	2	5	1.9	204	3	10	4.9	
1914.....	817	..	5	0.6	157	..	4	2.5	
1915.....	689	..	11	1.6	74	..	1	1.4	
(First ten months)									
Totals...	2493	13	32	1.3	2854	8	44	1.5	

It will be seen from the above table that the mortality after cholecystectomy is less at present than that after cholecystostomy

(1.2 per cent. as against 3.4 per cent.) for the last three years, or, including all cholecystectomies, 1.5 per cent.

In a series of form-letter inquiries sent to patients on whom cholecystostomy had been done during the past several years, none more recent than one year, 242 replies were received which showed that 53 per cent. of these patients were cured, 38 per cent. improved, and 9 per cent. not improved. Of the patients who were cured (129), 49 per cent. had stones, 11 per cent. had stones and empyema, 18 per cent. had stones and cholecystitis, and 22 per cent. had cholecystitis.

In a series of form-letter inquiries sent to patients on whom cholecystectomy had been done during the past several years, none more recent than one year, 219 replies were received which showed that 71 per cent. of the patients were cured, 22 per cent. improved, and 7 per cent. not improved. Of the patients who were improved (48), 57 per cent. had stones and cholecystitis and 43 per cent. had cholecystitis alone.

CONCLUSIONS

Cholecystitis is an infective disease of the gall-bladder. The bacteria are in the tissues of the gall-bladder.

Infection may be mild, acute, chronic, or recurring.

Gall-stones may occur in mild infections.

Gall-stones may cause mechanical obstruction.

Cholecystostomy (with removal of stones if present) gives a high percentage of cures only if the infection has subsided.

Cholecystectomy, with or without stones in diseased gall-bladders or existing cholecystitis, gives a high percentage of cures.

Reflex gastric symptoms are caused by the infection.

The infection may, through local peritonitis, cause adhesions to the bowels, stomach, or liver to abdominal wall.

Symptoms of mild gastric trouble may be nearly constant, may increase with exacerbation of infection and subsidence of attack, much like those of ulcer.

The etiologic factor may be a small local focus primary in the mouth, secondary in the appendix.

Typhoid bacteremia may also be the etiologic factor.

RESTORATION OF THE BILE-PASSAGE AFTER SERIOUS INJURY TO THE COMMON OR HE- PATIC DUCTS *

WILLIAM J. MAYO

The union of the cystic and hepatic ducts forms the common bile-duct. The juncture does not occur in a fixed manner, at a fixed point, but its location varies in different persons. It may lie close to the fissure of the liver or at any point between the liver and the duodenum. The normal situation is about three-quarters of an inch from the intrahepatic portion of the hepatic duct. When the point of union is low, the cystic duct may, and usually does, lie parallel and adjacent to the hepatic duct. If found in this anomalous position, the two ducts must be carefully separated in performing cholecystectomy in order to avoid the possibility of severing the hepatic duct.

In removing the gall-bladder it should also be remembered that the cystic duct has its origin on the posterior wall above the lowest point, and that the pelvis of the gall-bladder usually overlaps the cystic duct on its inferior and inner aspects. Quite frequently there is a little fold of peritoneum connecting the pelvis of the gall-bladder with the gastrohepatic ligament over the common duct, forming a small suspensory ligament. When this fold is present and is associated with marked inflammation, there are often many adhesions in the little triangle thus formed. Since the fold lies in a line with the cavity of the gall-bladder, it may be mistaken by the inexperienced operator for the cystic duct, and the common or hepatic duct may be completely severed. In

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some instances a section of the duct has been removed. To avoid this accident the pelvis of the gall-bladder should be carefully



Fig. 97.—Relation of gall-bladder to cystic, hepatic, and common ducts. Note cystic duct lying on the inner side and overlapped by the pelvis of the gall-bladder, which is shown drawn upward by the forceps.

dissected from the triangle until the cystic duct is fully exposed, ligated, and divided (Fig. 97).

The cystic artery usually passes behind and not along the cystic duct to the gall-bladder. The relation of the artery to the duct is almost like that of a bow-string to a bow, as it is shorter than the duct and lies on a plane closer to the liver. It sometimes happens, therefore, that the duct is securely grasped without catching the artery and, when the tissues are divided, the artery quickly retracts and bleeds freely. Hurried attempts to catch the artery with heavy rat-tooth forceps may result in serious injury to the great duct. When cut, this artery retracts into a pocket in Calot's triangle, and the forefinger, properly placed, will check the bleeding at once. A few mouse-tooth forceps can be caught in the tissues about the forefinger, forming a little basket, and by lifting on the forceps the finger can be removed and the artery caught with exactitude.

Brewer¹ has shown that the cystic artery occasionally originates in the superior pancreaticoduodenal artery instead of in the hepatic, and thus passes along the common and cystic ducts. In this location, however, it is easy to control if the anatomic situation of the vessel is recognized.

Judd's² method of carefully catching the cystic duct and artery, exposing them together, and separating them from the notch of the liver while sealed in their connective tissue, can ordinarily be employed, and it obviates any danger of injury to the common and hepatic ducts.

It is the general experience (Jacobson³) that injuries to the common and hepatic ducts are usually the result of various operative accidents. In the large majority of cases the accident is not discovered at the time of the operation, but only after the patient has developed a permanent biliary fistula or jaundice and other symptoms of obstruction. In a small minority the obstruction is the result of cicatricial tissue from gall-stone ulceration. Such obstructions are more frequently due to stones impacted in the cystic duct at the juncture of the common duct than to stones in the common duct itself. The free portion of the common duct has an extraordinary capacity for dilatation which is not true of the cystic duct. Ulceration does occur from stones within the common duct

and leads to the formation of stricture, but in our experience such strictures have been found in that portion of the common duct which is fixed in the head of the pancreas.

Benign tumors of the stump of the cystic duct may occur after cholecystectomy and cause obstruction of the common duct. There have been two examples in our clinic of true fibro-adenomas of the remaining portion of the cystic duct subsequent to cholecystectomy. The tumors were nearly the size of a hazelnut and more or less encapsulated. They caused typical symptoms of common duct obstruction with the syndromes of Charcot; *i. e.*, colic, fever, chilly sensations, and exacerbations of jaundice. Both patients were cured by removal of the tumor and the stump of the cystic duct (Fig. 98).

Operations for the restoration of the common bile-duct are usually of a formidable nature, not only because of difficult technic, but because of the poor condition in which these patients come to the surgeon. As a result of the former operation and continuation of the local irritation, there are always extensive adhesions, and in these adhesions are an unusual number of thin-wall veins which tear readily and flood the field with blood or keep up a continuous oozing, thus adding to the difficulties of the operative procedure.

The cystic and common ducts lie very close to the median line, and as the operation of cholecystectomy is the one that is now usually employed, the incision, whether for primary or secondary operation on the biliary tract, should be made rather close to the midline, probably not more than two inches to the outer side. Bevan's⁴ incision is most appropriate in the secondary operation. It begins at the ensiform cartilage, extends directly downward for one and one-half inches, then divides the upper half of the right rectus muscle on a line with the costal margin and about one inch from it. The longitudinal part of the incision should, if possible, be kept inside the original incision. All the bleeding vessels must be ligated, as they have a strong tendency to bleed after the operation, even when they are quite small. It is especially important to tie the vessels situated in the subcutaneous tissues and skin;

vessels in the muscles have less tendency to bleed after temporary clamping.



Fig. 98.—Adenofibroma of the stump of the cystic duct after cholecystectomy, causing common-duct obstruction.

Excision or Resection of the Obstructed Portion of the Common Duct, with End-to-end Union.—The strictured portion of the duct is

usually in the vicinity of the juncture of the cystic and common ducts and is from one-fourth to three-fourths of an inch in length; at least these have been about the extremes in cases we have operated on. Resections of this character demand rather exact technic. Adhesions are divided carefully and ligated rather than separated. The duodenum and stomach will be found adherent to the gall-bladder notch, often completely overlying the common duct. This necessitates dissection of these structures until the margin of the gastrohepatic ligament can be identified. The foramen of Winslow is cleared and the second portion of the duodenum, if overlying the strictured area, is dissected from its position. There will be little difficulty in identifying the hepatic duct by the telltale bile escaping from the fistula, if there is one, or by an opening made into the stump of the hepatic duct in the course of the dissection. It is surprising how easily the common duct may be found simply by carrying the dissection from the end of the hepatic duct directly through the strictured area along the margin of the gastrohepatic ligament. One would expect the distal end of the common duct to be contracted, but even after many months of complete obstruction it will be found normal in size. The stricture is dissected out until the ends of the hepatic and common ducts lie free; then several chromic catgut stay-sutures are introduced, catching the tissues behind the duct-ends which, when tied, obliterate the posterior space and draw the hepatic and common ducts into position for suturing. A few catgut through-and-through sutures are placed so as to unite the duct-ends posteriorly. The open end of the common duct is split along the anterior surface one-third of an inch, as advised by C. H. Mayo⁵ (Fig. 99). The split in the free border of the common duct increases its caliber to a considerable extent; it is thus more readily coaptated to the dilated hepatic duct. A "T" tube of appropriate size is now introduced, one arm extending about one inch into the hepatic duct to the primary division, and the other arm, if possible, through the entire length of the common duct until its free end passes into the duodenum (Fig. 99). The gap is closed about the "T" tube with chromic catgut sutures, the tube fastened with an absorbable

suture to the hepatic and common ducts, respectively, and the line of union covered by such omental and peritoneal tissues as may be available for the purpose. With a syringe, normal salt solution is forced through the "T" tube until it passes freely into the duodenum (McArthur⁶), and a few rubber-tissue drains are appropriately arranged. If possible, gauze should not be introduced in any form down to the line of union, as it tends to the formation of fistulæ. If necessary, a piece of rubber tubing may be



Fig. 99.—End of common and hepatic ducts sutured with through-and-through chromic catgut. Dotted line shows where the end of the common duct is enlarged by short longitudinal incision.

placed in Morison's pouch in the right renal area and carried out through a stab-wound in the loin. As a rule, when the "T" tube is used for reconstructions of the common duct it is not removed for about three weeks, at which time firm union will be established.

Strictured Area of the Common Duct Divulsed with Dilating Forceps.—For those cases in which the stricture is in the pancreatic portion of the duct, the result of ulceration, it has been found satisfactory to open the common duct and pass a pair of dilating forceps through the strictured area until it is completely divulsed. Stric-

tures in this vicinity are usually of the character of a diaphragm, and will often pop like paper on passing forceps through them into



Fig. 100.—"T" tube in place. Duct-ends sutured about it.

the duodenum. In the more difficult cases it will occasionally be found necessary to open the duodenum and expose the papilla

before undertaking divulsion of the stricture. After divulsion, a "T" tube is placed in the duct, one arm of the tube being sufficiently long to pass completely into the duodenum.

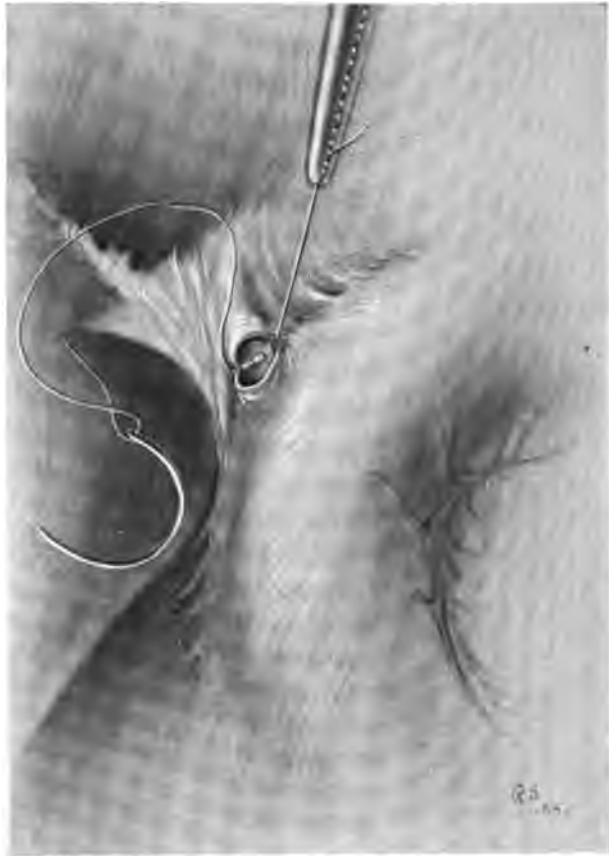


Fig. 101.—Direct union of hepatic duct to duodenum. Gall-bladder has been removed. Continuous chromic catgut sutures have been placed uniting posterior wall. The stay sutures, holding hepatic duct to duodenum, of interrupted chromic catgut, lie behind this suture and are not shown.

Extensive Injuries to the Great Bile-duct Necessitating Union of Hepatic Duct to the Duodenum.—In the more extensive injuries it may be necessary to suture the hepatic duct directly to the duodenum. The first patient operated on in our clinic was reported in

1905,⁷ and the woman is well now after more than ten years. It is of interest that since the operation she has borne several children and has had some severe illnesses, not, however, connected with the biliary tract.

Two-row Suture Anastomosis.—In our experience in these cases the stomach and duodenum have been found closely adherent to the site of the injury. If care is used not to separate these adhesions too extensively, the duodenum may be so closely approximated to the dilated hepatic duct as to secure a two-row anasto-

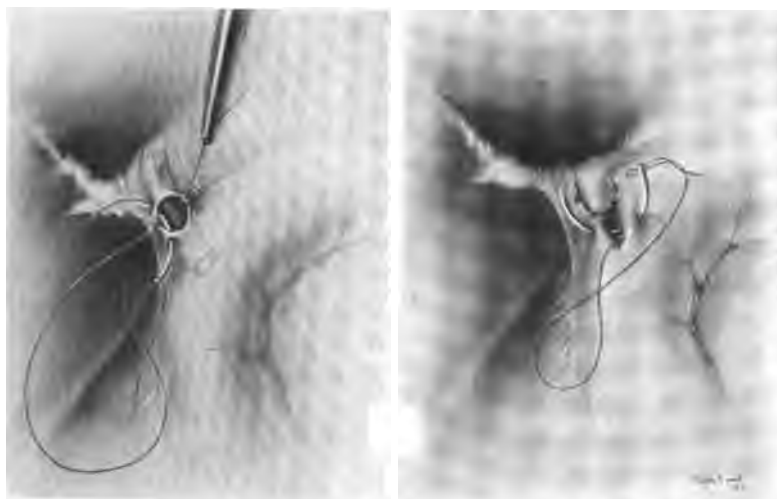


Fig. 102.—Rubber tube in place and fastened by chromic catgut suture to the hepatic duct. Anterior layer of chromic catgut continued. Duodenum being sutured to enfold anastomosis, the area later to be covered by omentum.

mosis without great difficulty on the general principles of gastrointestinal union, the omentum being carefully sutured around the anastomosis with fine chromic catgut. In one case in which there was a contracted gall-bladder about one inch in length it was possible to make a pedunculated flap of the gall-bladder and fill in a considerable gap, thus bridging a defect which the duodenum could not be mobilized sufficiently to overcome. In another instance a small flap was dissected from the duodenum in a manner somewhat similar to that carried out by Walton.⁸

Union by Rubber Tube of the Common or Hepatic Duct to the Duodenum.—To Sullivan⁹ belongs the credit of having shown the possibility of uniting the hepatic or common duct with the duodenum by means of a rubber tube, and leaving it as a more or less permanent connecting link surrounded by omentum. This is by all means the simplest method of restoring the bile-channel, but unfortunately the newly formed channel is not mucus-lined, and we must expect that eventually contraction will take place after the rubber tube slips into the intestine, which will ultimately occur. However, we have not found it difficult to combine this method with direct union of the hepatic or common duct to the duodenum, and results with this combined operation have been excellent.

Technic of the Procedure.—The hepatic duct is united as well as possible by a mucomucous suture to an opening made into the duodenum and a rubber tube introduced and sutured into position. The suture is continued in a manner so that at least some portion of the new canal may be mucus-lined. The line of union is, of course, not bile-tight, but by surrounding it with omentum it does not seem to leak into the peritoneal cavity. The tube extends into the hepatic duct to the primary division and about one inch into the duodenum. After absorption of the holding sutures, the rubber tube readily passes into the intestinal tract. This is the operation of choice in the majority of cases, and a number of our patients have been cured by it (Figs. 101 and 102).

Direct Union of the Common Duct to the Duodenum.—This method has been used in our clinic several times following resection of the common duct for cancer and once following partial gastrectomy for cancer of the pyloric end of the stomach. After removing the involved portion of the common duct the distal end is tied, the stump covered with peritoneum, and the proximal end united to the duodenum after the method of Coffey. The method is applicable in primary operations when the liver-end of the duct is easily accessible; in secondary operations there are, as a rule, so many adhesions that the duct cannot be sufficiently mobilized to accomplish it. Our experience in resections of the common duct for

cancer in restoration of the biliary channel by any method has been discouraging. Two of these patients died soon after operation and those who recovered lived less than eighteen months; in none of them, however, was death directly associated with this particular feature of the operation.

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PATHOGENESIS OF SPONTANEOUS AND EXPERIMENTAL APPENDICITIS, ULCER OF THE STOMACH AND CHOLECYSTITIS *

EDWARD C. ROSENOW

Although the infectious nature of appendicitis, of cholecystitis, and, to a large extent, of ulcer of the stomach is now quite generally conceded, there is still much speculation as to the exact mechanism of the occurrence of each, and especially as to the supposed etiologic relationship between them. They are still believed to be due either to surface infection from the lumen, aided by various mechanical factors, such as foreign bodies and spasms, or to migration of the bacteria through the lymphatics, even against the normal lymph-stream, and only rarely to embolism from some distant focus, such as infected tonsils, pyorrheal pockets, or the intestinal tract. That these organs are developed from a small segment of the primitive alimentary tract and that irritation of the colon (Cannon) and disease in the appendix or gall-bladder, for example, will reflexly cause delayed emptying of the stomach and hyperacidity with the accompanying symptoms is believed by some to account for the fact that two or more of these organs may be diseased simultaneously (Cannon,¹ Litthauer,² Mayo,³ MacCarty,⁴ Billings,⁵ Graham and Guthrie,⁶ LaRoque⁷). The reason for the lack of exact knowledge as to their origin is due largely to a study of end-results in patients, and not enough of experimental study in animals.

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I wish to call attention briefly to certain results following intravenous injection of streptococci which seem to throw some light on the mode of origin and pathogenesis of appendicitis, ulcer of the stomach, and cholecystitis.

The technic employed and the details of the experiments in appendicitis have already appeared,⁸ and those on ulcer and cholecystitis will appear shortly.

ELECTIVE LOCALIZATION OF STREPTOCOCCI FROM APPENDICITIS, ULCER OF THE STOMACH, AND CHOLECYSTITIS

SOURCE OF STREPTOCOCCI	TIME OF USE	STRAIN	ANIMALS INJECTED	PERCENTAGE OF ANIMALS SHOWING LESIONS IN					
				Appendix	Stom.		Duod.	Gall-bladder	Pancreas
					Hem.	Cl.			
Appendicitis	When isolated	14	68	68	6	1	1	0	9
	Later	8	26	15	19	15	4	0	0
	After animal passage	7	22	45	45	30	40	0	20
Ulcer of stomach in man	When isolated	18	103	2	60	60	20	3	7
	Later	8	22	5	5	0	5	0	0
	After animal passage	7	59	0	23	33	30	15	15
Cholecystitis	When isolated	12	41	0	29	15	80	5	17
	Later	5	14	14	28	14	7	0	0
	After animal passage	4	16	0	31	13	56	19	13
Average per cent. of animals showing lesions in these organs exclusive of specific strains				5	20	9	11	6	8

The accompanying table gives the incidence of lesions in the appendix, stomach, and duodenum, gall-bladder, pancreas, and intestines in animals following intravenous injection of streptococci from appendicitis, ulcer, and cholecystitis, when first isolated, after cultivation on artificial media for some time and after animal passage. In the last line is given the average percentage of animals showing lesions in these organs following the injection of numerous strains of streptococci into many animals exclusive of the specific strains, and serves for comparison. It is seen that 14 strains from appendicitis produced lesions in the appendix in 68 per cent. of the 68 rabbits injected, which is in marked contrast

to an average of only 5 per cent. of lesions in the appendix in the animals injected with the strains as isolated from sources other than appendicitis. Eighteen strains from ulcer of the stomach or duodenum produced hemorrhage in 60 per cent., and ulcer of the stomach or duodenum in 60 per cent., a combined total of 74 per cent. of the 103 animals injected, in contrast to an average of 20 per cent. hemorrhages and 9 per cent. ulcers following the injection of other strains. Twelve strains from cholecystitis produced lesions of the gall-bladder in 80 per cent. of the 41 animals injected, in contrast to an average incidence of only 11 per cent. of the other strains.

The streptococci with which these results were obtained were mainly isolated from the involved tissues or from the lymph-glands draining the area, and were removed during life in the operating-room. A number of strains from each, however, were obtained from the apparent infection-atrium. In acute appendicitis the peculiar affinity of the streptococci in the focus was present only at the time of the attack and disappeared promptly later, while in one case of chronic ulcer of the stomach it was found present over a period of six months. The strains resemble each other very closely indeed, those from appendicitis, however, being the least virulent, those from ulcer occupying a middle position, and those from cholecystitis being the most virulent. It has been suggested that the localization in these organs of bacteria so nearly alike may be due, in a measure, to the fact that they are derived from the same segment of the primitive alimentary tract affording, as it were, a common soil.

From studies of the effect of animal passage on non-virulent "laboratory" strains of streptococci, it was found that virulence appeared to be a factor in determining the place of survival of streptococci on intravenous injection. If the localization is related to virulence, then the incidence of the occurrence of ulcer and cholecystitis should become greater as the appendicitis strains are passed through animals, and appendicitis should occur oftener after the ulcer and cholecystitis strain loses virulence on cultivation on artificial media. This is found actually to be the case. Thus,

the strains from appendicitis, on isolation, produced ulcer of the stomach or duodenum and lesions in the gall-bladder in 1 per cent. of the animals, whereas after animal passage lesions occurred in 30 and 40 per cent. respectively; the ulcer strain produced lesions in the gall-bladder in 20 per cent., when isolated, and in 30 per cent. after animal passage.

The more frequent occurrence of pancreatitis and cholecystitis, or pancreatitis and ulcer of the stomach or duodenum, than of appendicitis and pancreatitis, is well known. Since lesions of the pancreas following injection of the strains from ulcer and cholecystitis as isolated (3 per cent. and 5 per cent.), and especially after animal passage (15 per cent. and 19 per cent.), are more common than following injection of those from appendicitis, it might be suggested that the reason for more frequent occurrence in man of pancreatitis with ulcer and cholecystitis is due partly to the fact that the infecting organisms are more nearly of the grade of virulence necessary to infect the pancreas, and not wholly due to the greater proximity of the organs. And why might not the greater severity of symptoms and the more frequent occurrence of fatal peritonitis following surgical intervention in pancreatitis, cholecystitis, and after perforation in gastric ulcer than in appendicitis be due to the greater virulence of the infecting streptococcus or other bacteria more than to the fact that they are situated in the upper portion of the peritoneal cavity, as is now generally believed? The fact that the virulence of the strains having elective affinity for the appendix is low is undoubtedly an important factor in the successful surgical treatment of appendicitis. If this were not so, strangulation and perforation, so prone to occur, would lead almost always to a fatal peritonitis. It might be suggested, too, that the real cause of a fatal peritonitis, with or without surgical intervention, is due more often to invasion by particularly virulent bacteria than to other factors, such as slight variations in operative technic.

The occurrence of lesions in the intestines following injection of the strains from appendicitis (9 per cent.), ulcer of the stomach (7 per cent.), and cholecystitis (17 per cent.) is due partly to the large doses injected, but even then it is probably little greater than could

reasonably be expected in the spontaneous disease in man, could a thorough search for them be made. Here, again, the incidence of lesions tends to become greater on animal passage. It should be stated here that in some instances colon bacilli from the appendix in appendicitis and the gall-bladder in cholecystitis showed a similar elective affinity for the organ from which isolated when injected in animals.

From these results the conclusion seems warranted that appendicitis, ulcer of the stomach and duodenum, and cholecystitis are largely embolic infections from some distant focus of infection, or even from the more or less normal intestinal tract, by streptococci or other bacteria having elective affinity for these structures, and that the simultaneous presence of two or more of these diseases in the same individual is in the beginning due more often to this cause and not so often to infection by continuity or by way of the lymphatics. Finally, since these bacteria can be made to shift in their localization by cultivation on artificial media and by animal passage, and because the peculiar affinity of the strains in the focus is present only at the time of the attack, it is highly probable that the so-called focus of infection is not only the place of entrance, but the place where opportunity is afforded for bacteria to acquire the various affinities necessary to infect. Hence the importance of a thorough search for the presence of foci of infection and their eradication if possible. In other words, the presence of appendicitis, and especially of ulcer of the stomach and duodenum, and cholecystitis are to be considered good evidence for the existence of some distant focus of infection, and, because these lesions may act as secondary foci, drainage or surgical removal of the diseased tissue, if this can be done with little risk, is undoubtedly a most rational treatment.

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AN EPIDEMIC OF APPENDICITIS AND PAROTITIS, PROBABLY DUE TO STREPTOCOCCI CONTAINED IN DAIRY PRODUCTS *

EDWARD C. ROSENOW AND STELLA I. DUNLAP

The occurrence of appendicitis in epidemic form, its seasonal prevalence, and its occurrence in several members of the same family have been noted repeatedly (Mantle,¹ Hood,² Martin,³ Wahle,⁴ Haim,⁵ and Rostouzew⁶).

The epidemic of appendicitis and parotitis studied by us occurred at the Culver Military Academy, Culver, Indiana.† From February 21 to March 5, 1915, a period of twelve days, there occurred eight cases of acute appendicitis; two cadets developing appendicitis on the same day. Seven of the eight patients were operated on and the diagnosis verified. All recovered. Only seven cases developed during the rest of the school year—two in October, one in January, three in April, and one in May.

Previous to the sudden outbreak of appendicitis two cadets developed parotitis. During the prevalence of appendicitis 5 developed parotitis, while during March and April there occurred 27 cases. In May only 3 developed parotitis, making a total of 34 cases. From April 10 to 18 there occurred an average of one new case a day, and on April 25 three students developed the disease. During the epidemic of parotitis 3 cadets developed appendicitis. The parotitis was not limited to the cadets whose ages

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† The study was made at the request of the superintendent of the academy, Lieutenant-Colonel L. R. Gignilleat. We wish to express our appreciation to him for the opportunity and to Dr. C. E. Reed for much aid in the work.

ranged from fifteen to nineteen years, but occurred in several older persons as well.

The occurrence, character, duration, and complications of the parotitis were typical of mumps. The epidemics occurred without associated tonsillitis. The cases of appendicitis were so distributed among the population as to rule out the factor of trauma from violent exercise.

The total number of persons at the academy who ate in a common dining-room of the same food was approximately 500. Of these, 430 were cadets ranging in age from fifteen to nineteen years; 30 were members of the faculty; 40 were helpers, and had to do with the preparation and serving of the food, etc. On investigation the sanitary conditions, the refrigerating plant, the kitchen and dining-room, the apparent quality of food served and method of handling it, of the mode of life as to exercise, etc., the general physique and health of the cadets, were all found to be excellent.

The dairy products consumed were obtained from four independent sources. The milk and cream and the ice-cream served at the mess were from a number of dairies directly under the supervision of the authorities at the academy. These dairies were kept in first-class condition, the milk cooled soon after milking, and refrigerated continuously until used. The butter, of first-grade quality, was an Indiana product from a neighboring town. The cheese was from southern Wisconsin. The ice-cream served to many cadets at a neighboring shop was found to be prepared from cream obtained from local dairies under unsanitary surroundings, and with deficient refrigeration. Pasteurization was not practised.

Since virulent streptococci have been isolated frequently from the udders of cows with mastitis, and even from normal udders in model dairies (Rosenow⁷), and since epidemics of "septic sore throat," scarlet fever, and typhoid fever have been traced to milk, the possibility that these epidemics were due to bacteria in the dairy products had to be considered. Cultures and animal inoculations were therefore made of the milk, cream, butter, and cheese which were for general consumption at the mess, and the

ice-cream which was consumed by the cadets at the neighboring shop. A similar study was also made of cultures obtained from the tonsils of cadets, members of the corps who prepared and served the food, and members of the faculty and of those that developed appendicitis.

Technic.—The technic of making the cultures and animal inoculations was similar to that described by me in connection with the production of appendicitis.⁷ The cultures from the cases of parotitis were made by catheterizing Steno's duct of the involved gland and from the tonsils. The bacteriologic study consisted in the main of making blood-agar plates and inoculations into a series of tall columns of ascites (10 per cent.)-dextrose (0.2 per cent.) broth of the material examined. These were incubated at 37° C. over night, the character of the growth on the plates noted, smears of the cultures in broth made, and those free from bacilli or in which there were only few to be found, injected intravenously into rabbits and dogs.

The sediment of from 50 to 200 c.c. of milk and cream was used for the inoculations of the media. The butter and cheese (approximately 0.5 c.c.) obtained in a sterile manner from the depth of a freshly cut surface of the original package were emulsified in 2 c.c. of sodium chlorid solution and then planted. An attempt was made to obtain material from the depth of the tonsils, and not merely by swabbing the surface. The bacteria for injection were suspended in salt solution, so that 1 c.c. contained the growth from 15 c.c. of the broth culture. A portion of the suspension injected was again plated on blood-agar. The animals, often injected in series with doses ranging from 1 to 6 c.c., were chloroformed usually in forty-eight hours if they did not die from the effects of the injection. The postmortem examinations were made as soon after death as possible. The organism responsible for the lesions was determined by culture and sections.

RESULTS OF INVESTIGATION

Sections have been made from four of the human appendices. All showed streptococci in the tissues and some in almost pure

culture. Cultures both from the tonsils and from the wall of the appendix were made in one patient. The culture from the tonsils showed a predominating number of short-chain, green-producing streptococci, a few hemolytic streptococci, and a moderate number of *Micrococcus catarrhalis*, and those from the wall of the appendix showed colon bacilli and green-producing streptococci. The culture in ascites-dextrose broth from the tonsils of this patient was injected into three rabbits. All remained well, and none showed

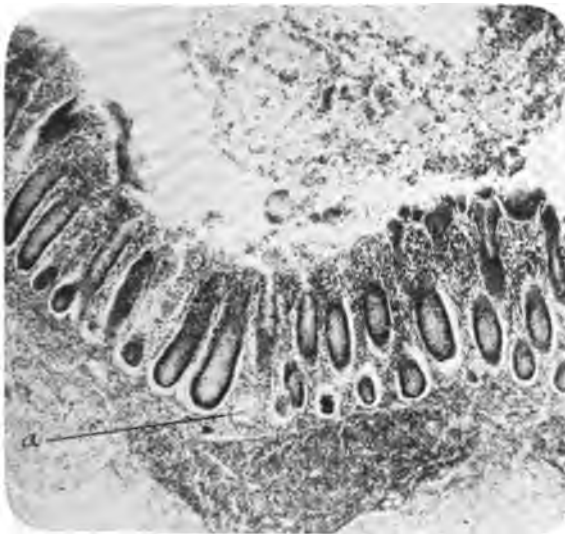


Fig. 103.—Section of appendix in human appendicitis. Note the sloughing of the mucous membrane, the hemorrhagic and leukocytic infiltration in the lymph-follicle, mucous membrane, and submucosa. Hematoxylin and eosin.

lesions in the appendix. The growth from the wall of the appendix produced lesions in the appendix in two out of four rabbits.

The findings in the following patient will further illustrate the results obtained:

Mr. M., one of the cadets who developed symptoms of acute appendicitis February 21, was operated on the following day and the acutely inflamed and edematous appendix removed. On examining the appendix the lumen was found to be very narrow and

filled with bloody pus. There was no fecal concretion or other foreign body nor constricting bands. The peritoneal coat was edematous and opaque, and over the portion near the distal end was found a thin, fibrinous exudate. The mucous membrane was edematous and hemorrhagic throughout the larger portion, and microscopic examination showed this to extend well into the submucosa and peritoneal coat, the muscular coat being quite normal. Sections showed an enormous number of streptococci within the lumen and within the infiltrated mucous membrane (Figs. 103 and 104). Scattered diplococci were found also in the adjacent lymph-

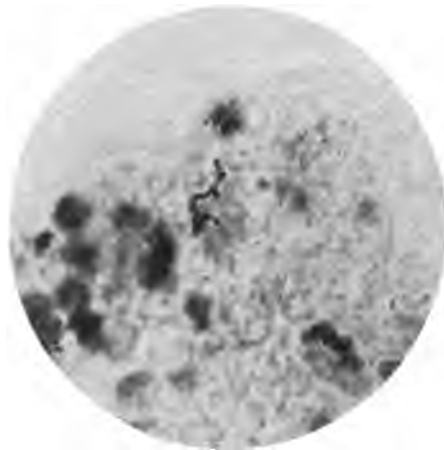


Fig. 104.—Streptococci in submucosa at a, shown in Fig. 103. Gram-Weigert ($\times 1200$).

follicles and peritoneal coat. In the lumen there were found also a few Gram-negative bacilli resembling colon bacilli, and what appeared to be fusiform bacilli. Cultures from a swab of the tonsils sent me by Dr. Reed ten days after the operation showed a predominating number of green-producing streptococci, a few colonies of hemolyzing streptococci, and a large number of colonies of *Micrococcus catarrhalis*. The broth culture showed a pure growth of a short-chain streptococcus. Two rabbits were injected with the latter culture, one of which showed hyperemia and hemorrhages in the mucous membrane and peritoneal coat of the appendix;

the other did not. The former showed a few hemorrhages in the tricuspid valve in addition; the latter, slightly turbid joint fluid. The cultures from the blood of both showed pure cultures of green-producing streptococci on blood-agar plates. The emulsion of one of the areas of hemorrhage in the peritoneal coat of the appendix showed many green colonies of streptococci.

On June 4th cultures from the tonsils were again made. They were found larger than normal, but not badly infected. The culture in ascites-dextrose broth was injected into one rabbit, which developed a number of small hemorrhages in the appendix, with hyperemia and edema, as well as a marked hemorrhagic edema of the parotid and associated lymph-glands. There were also found a number of hemorrhages in the muscles, particularly in the adductors of the thighs. The localization in the parotid is of interest, especially since this individual was the janitor in the hospital in which the patients with parotitis were treated and would have to be considered a carrier.

LOCALIZATION OF STREPTOCOCCI FOLLOWING INTRAVENOUS INJECTION

SOURCES OF STREPTOCOCCI		TIME OF EXPERIMENTS	ANIMALS	STRAINS	PER CENT. OF ANIMALS SHOWING LESIONS IN	
					Appendix	Parotid
Tonsils	Normal persons	Soon after epidemic of appendicitis (March)	49	43	30	10
		Soon after epidemic of parotitis (June)	30	30	6	20
	Persons having had appendicitis	Soon after epidemic of appendicitis (March)	19	4	47	0
Dairy Products	Soon after epidemic of appendicitis (March)		22	9	41	9
	During epidemic of parotitis (March and April)		28	8	0	29
	Soon after epidemic of parotitis (June)		10	6	0	30
Steno's Duct in Parotitis	During epidemic of parotitis (March and April)		19	9	15	73

The table gives a summary of the results obtained following intravenous injection of streptococci isolated from tonsils, dairy products, and Steno's ducts. It will be seen that the cultures obtained from the tonsils of normal persons soon after the epidemic of appendicitis and at the beginning of the epidemic of parotitis produced lesions of the appendix in 30 per cent. and in the parotid gland in 10 per cent. of the animals injected. After the epidemic of parotitis, cultures made in exactly the same way produced lesions in the appendix in 6 per cent. and in the parotid in 20 per cent. of the animals injected. The lesions in the appendix here correspond with the average incidence of lesions in the appendix (5 per cent.) following injection of streptococci from a wide range of sources. The cultures from the tonsils in persons having had appendicitis soon after the epidemic of appendicitis, produced appendicitis in 47 per cent. of the animals injected and no lesions in the parotid. The dairy products soon after the epidemic of appendicitis, including cultures made up until March 19, produced lesions in the appendix in 41 per cent. and in the parotid in 9 per cent. of the animals injected, while during and soon after the epidemic of parotitis the strains failed to produce appendicitis, but produced parotitis in 29 and 30 per cent., respectively, of the animals injected. The streptococci obtained from patients having parotitis during the epidemic produced lesions in the appendix in 15 per cent., and in the parotid in 73 per cent. of the animals injected.

In this connection it should be noted that four of the six persons whose tonsils were cultured and who had to do with the serving of food, including the waiter of the table where two cadets developed appendicitis on the same day, showed streptococci having affinity for the appendix of rabbits. One of these is subject to repeated mild attacks of appendicitis.

The average incidence of lesions in the various organs and the mortality rate in the animals injected with the cultures from the tonsils or throats of 46 normal persons during March was 14 and 41 per cent. respectively, while during June it was only 8 and 33 per cent. respectively. The evidence of infection in the tonsils

was distinctly greater during March, although none complained of sore throat and in none was the inflammation acute.

The occurrence of lesions was greater in the animals injected with the cultures from distinctly infected tonsils (18 per cent.) than in the animals injected with the cultures from the more normal tonsils or the normal throats (four) in which there had been a previous tonsillectomy (10 per cent.).

Likewise there was a distinctly higher incidence of lesions and greater mortality rate following injection of the streptococci from the dairy products during March and April, 11 and 26 per cent. respectively, than during June, 8 and 10 per cent. respectively. These findings suggest that the seasonal prevalence of streptococcal throat infections is due largely to an increase in infective power of streptococci in tonsils, and possibly in dairy products as well.

It must not be supposed that the lesions in the appendix and parotid are merely accidental. Cultures from the milk and cream produced lesions in the appendix on March 6th and 19th, while those injected on March 13th, April 25th, and June 4th failed entirely to produce lesions. In only one rabbit did the cultures from the milk and cream produce parotitis (March 12th). Cultures from the butter, made March 5th and 13th and on April 9th and 25th and June 4th, did not produce lesions in the appendix, while lesions in the parotid were produced in rabbits following injection of cultures from all the samples obtained on the four latter dates. The cultures from the samples of butter obtained on April 9th showed a large number of two types of colonies of streptococci: the one produced distinct green colonies on blood-agar, the other produced smaller, grayish, elevated, round colonies surrounded by a narrow, hazy zone of hemolysis. Injections of the mixture produced marked edema and hemorrhage of the parotid in both of two rabbits. Pure cultures of the latter (second culture) produced marked edema of the parotid and hemorrhage of the parotid in two out of three rabbits. The strain which grew in pure culture in dextrose broth produced similar lesions in both of two rabbits, and the swelling and cellular infiltration considered characteristic of mumps

were produced in each of three dogs, after injection into Steno's duct.* The cultures from the cream and ice-cream supplied at the neighboring shop produced many lesions of the appendix in both of two rabbits injected March 19th, while cultures on two subsequent occasions after the plant was remodeled failed to produce either appendicitis or parotitis. Cultures from the cheese failed to produce either appendicitis or parotitis on March 15th, but produced appendicitis on March 13th, parotitis on April 25th and on June 4th. Cultures made May 7th and June 4th from butter and ice-cream from another source failed to produce either appendicitis or parotitis. Investigation showed that mumps was present in epidemic form in the communities where the butter and cheese was manufactured during April and May—the time parotitis was so prevalent at the academy and the time when there was found in them streptococci having such marked affinity for the parotid gland. The possibility of infection at the academy of the butter and cheese with these strains is excluded, because the cultures were made from the original packages, but whether these strains were from human sources or were from the udder of the cows is impossible to say. It might be said, however, that the fermentative powers of some of the strains having affinity for the appendix suggest the latter origin, while those producing parotitis had fermentative powers suggesting the former source.

The cultures from the dairy products showed a preponderance, often in almost pure form and in enormous numbers, of non-hemolyzing, short-chain-producing streptococci. Slightly hemolyzing streptococci were found occasionally. All were of a relatively low grade of virulence, but those producing parotitis caused death more frequently than those producing appendicitis.

The importance of the streptococci contained in the dairy products as a possible source of infection for man is further shown by the fact that 6 per cent. of the animals showed ulcer of the stomach, 6 per cent. cholecystitis, 28 per cent. arthritis, 6 per cent. endocarditis, 20 per cent. myocarditis, and 26 per cent. myositis. The high incidence of myositis and myocarditis, occurring two and

* The results of the experiments with the organisms from parotitis will be detailed in a separate paper.

five times as often as with streptococci from the tonsils, is of special interest, and is in accord with the findings of Rosenow and Moon,⁸ who showed that streptococci from milk during an epidemic of sore throat had a marked affinity for the muscles in animals.

The lesions other than those in the appendix and parotid following injection of the streptococci from the tonsils parallels very closely indeed those obtained previously by one of us with streptococci from similar sources. It is, of course, realized that liability to infection following ingestion of the streptococci by man is less than following intravenous injection in animals. Yet that it may occur must be conceded.

Normal persons (10 per cent.) during and immediately after the epidemic (20 per cent.) who harbored streptococci having elective affinity for the parotid in animals must be regarded as carriers.

It would appear then that these epidemics of appendicitis and parotitis were due to streptococci contained in dairy products. In view of this fact and the fact that milk is so excellent a culture-medium makes efficient pasteurization or some other means of destroying the pathogenic bacteria which may be present in milk imperative in order that the public health may be safeguarded.

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ACUTE PERFORATIONS IN ABDOMEN—TRAUMATIC, SPONTANEOUS *

WILLIAM J. MAYO

The question of acute perforations in the abdomen is an exceedingly important one, because in acute perforations we are at once confronted with one of the most serious accidents that can possibly happen to the patient. It is one in which the judgment exercised by the surgeon probably will determine whether that patient will live or die, yet a judgment for which there is comparatively little time for the surgeon to make up his mind, because that patient must be operated on at once if he is to be saved. This is true to a very large extent both of spontaneous perforations and of those perforations which are the result of traumatism.

Taking up, first, the question of the necessity of immediate operation: I have been very much interested in the reports that come from the battle-field indicating the changing opinion as to whether or not military gunshot wounds should be subjected to immediate operation. It has been claimed by military writers that gunshot injuries of the abdomen which are operated on did not show a better mortality rate than those in patients who were left without operation. But, as pointed out by a number of recent writers, the death-rate has been on the battle-field, the soldier who received the gunshot injury not being able to get back to the base hospital. Therefore the comparison was an unfair one. It was only those patients naturally selected by the nature of their injury who ever got back of the battle-line, and when they got back to the base hospital, the very fact that they had been able to live

* Stenographic report of address before the Chicago and Northwestern Surgical Association, December 10-11, 1915, Rochester, Minn. Reprinted from the *Railway Surgical Journal*, 1916, xxii.

forty-eight hours instead of dying on the battle-field made the difference, so that the real mortality rate should be studied not at the base hospital, among these patients selected by the nature of their injuries, and therefore much more likely to recover, but rather by taking note of all the injuries as they occur on the battle-line.

Summing it up in this way, several surgeons have shown that, considering, on the one hand, only those abdominal injuries occurring at the battle front in which operation has been done two, three, or four hours after injury, as contrasted with the total number of abdominal injuries, the mortality of the unoperated patients is nearly three times as great as the mortality of those operated on, provided the latter were operated on within six hours. Now, this is equally true both of perforations that are produced by traumatism and of spontaneous perforations. In spontaneous perforations there are a number of different circumstances entering into the question, such as the nature of the viscus that perforates, the character of its contents, and the amount.

We will consider here, on the one hand, spontaneous perforations of the stomach, duodenum, gall-bladder, appendix, and pancreas (which we speak of as fat necrosis); and, on the other hand, the traumatic perforations of the intestines and of the bladder. In addition to these there are perforations of tumors, etc., which I shall not discuss.

Taking, then, as our guide the most common type of perforation outside of the appendix—that of the duodenum: If we compare the results of perforations of the duodenum with perforations of the stomach, we find first that perforations of the duodenum are often followed by recovery. In perforation of the duodenum, with its relatively sterile contents, comparatively small in amount, the leakage may be small as contrasted with that from the stomach. Then, too, about the duodenum we have the gall-bladder, the liver, the suspensory ligament, and the transverse colon, all of which aid, so to speak, in plugging such leaks. Therefore we find that many patients with perforation of the duodenum get better, and that is also somewhat true of perforations near the pylorus. But when we

come to the stomach, with its large content and the absence of any organ close to it, except the pancreas, on the posterior wall, we find that free perforation of the stomach into the general peritoneal cavity is more fatal, because a much larger quantity of material escapes.

In our experience perforation of the gall-bladder has been one of the most fatal of the various forms of perforations. This is because the large majority of patients who have perforation of the gall-bladder have had previous attacks of gall-stone colic, in some cases prolonged for several days, and they are more apt to die when perforation occurs into the free peritoneal cavity, not because of the nature or quantity of the contents of the gall-bladder, for both of these would be comparatively insignificant, but because, as a rule, the patient will not be operated on for four or five days, feeling certain that the condition is nothing more than that of previous attacks.

As I remember, we have had this year four cases of acute simultaneous perforation of the gall-bladder and appendix into the general peritoneal cavity, the diagnosis being verified at the time of operation. Therefore when we find a perforation of the gall-bladder, it is always wise to look at the appendix. It may be that the perforation in the appendix comes first, the infection then being carried through the portal circulation to the gall-bladder, causing a necrosis of this organ also.

Perforations of the pancreas form an exceedingly fatal group, although we now know, from observations made in cases of fat necrosis occurring in patients who were operated on during a period when they were getting better, that a number of these cases do get well spontaneously—probably a much higher number than we have been aware of. Nature has been able to care for the infection, and the patient, after an illness that nearly took his life, was able to recover.

How are we going to know whether or not perforation has occurred? That is really the crux of the entire problem.

I take it that every one of us here believes that if perforation of a viscus has really taken place, then we should operate and operate

at once. Our experience, for instance, has been that patients with perforation operated on within the first eight hours have nearly all recovered, and that, as the time of operation progressed beyond that period up to twenty or twenty-four hours, a progressively higher percentage of patients have died. Curiously enough, after the first twenty-four hours the mortality improves again, for the reason that in those patients operated on early the peritoneum has been able to ward off infection to a reasonable extent. In the second period are similar cases in which infection has actually taken place, and I think that is why patients in the third period have gotten well in a larger percentage than have those in the second period—they were patients who, had they gone on a little further, would have had what we might call spontaneous cure; just as on the battle-field those who go on to a fatal termination are more liable to do so in the first twenty-four hours, while the patient able to live for four or five days before operation is thereby put in the favorable class.

There is one thing in common with all these cases which I believe will be of very great assistance to us in making up our minds whether or not a patient should be operated on; and that is the question of muscular rigidity. You will remember that the symptoms of perforation are, first, the sudden attack of pain, then faintness, nausea and vomiting, and then muscular rigidity. A curious thing about this muscular rigidity is that, if no hemorrhage takes place at the time of perforation, as often happens in traumatic cases,—such as the case of a man squeezed between a car and a wall, or a case such as I have seen within a comparatively short time, a neck-yoke breaking, coming back and striking the man in the abdomen,—in spite of the fact that there is perforation, if there be no hemorrhage, an improvement comes on after the initial period of shock. Yet this improvement is a fatal improvement. I do not know of anything that is so fatal as the improvement that takes place in a patient who has had a perforation, and, after a few hours, has recovered from the immediate effects, in whom the pain has disappeared, and who says, "Now I am all right." But is he all right? How can you tell? Has he muscular rigidity? If he is all

right, while ordinarily he will not be immediately relieved of pain, there should be no muscular rigidity. Any patient who continues to have muscular rigidity after the relief of pain from spontaneous causes we should operate on, basing our decision on the symptom of muscular rigidity.

I think, therefore, that continuation of muscular rigidity is the one thing that, in the second period, tells us whether the patient has perforation, and whether or not he should be operated on.

But is muscular rigidity one of those signs that is always present? It is not. There is a type of peritoneal cavity that is anesthetic. You all remember the great Swedish surgeon Lennander, and his work on the question of the sensitiveness of the peritoneum. He pointed out that the parietal layer is the more sensitive, but the visceral peritoneum is insensitive; unfortunately in some persons the parietal peritoneum is not sensitive. We have often seen patients—usually men about fifty, of considerable flesh, but not necessarily so—who have a colic, are quite ill for a few hours, who then take up their work, and perhaps at seventy-two hours are not very ill, yet when you open up the abdominal cavity of one of this type you find it full of pus. Therefore, let us put it this way: The continuation of muscular rigidity in a doubtful case is sufficient to warrant operation.

In connection with perforations of the bladder. I have happened to see several intraperitoneal perforations of the bladder, and the interesting thing about them is that, though they may take place with urine accumulating in the peritoneal cavity, the patient passing more or less urine, really out of the peritoneal cavity, yet the patient may go on in this condition for from five to twelve days with no peritonitis whatever, as you find at operation. This means that if the urine is sterile, there will be no immediate peritonitis. In these cases you may not have muscular rigidity—there may be simply an ascites.

In regard to these cases, remember this: When you do not know whether or not a man has intraperitoneal rupture of the bladder, get all ready to operate before you put a catheter or a sound into his bladder, because of the rapid infection which takes

place. No matter how sterile the catheter, no matter how sterile we believe the urethra to be, the mere introduction of an instrument under such circumstances into the bladder will probably be followed shortly by fulminating peritonitis. So if you are going to operate in case you find perforation, make your arrangements to operate at once following the determination that perforation does exist.

SUBDIAPHRAGMATIC ABSCESS *

EDWARD STARR JUDD

A subdiaphragmatic abscess may be designated as a collection of pus situated immediately below, and in contact with, the diaphragm. This subdiaphragmatic space is divided into four intraperitoneal anatomic subdivisions and two extraperitoneal cellular spaces. The four intraperitoneal spaces are separated from one another by the cruciform arrangement of the ligaments of the liver. The falciform ligament divides the subphrenic space into a right and a left compartment, and each of these compartments is again subdivided, by the coronary and corresponding lateral ligament, into a large anterior and a small posterior part.

The right extraperitoneal subphrenic space is between the layers of the coronary ligament. The left extraperitoneal space begins in the perinephritic tissues around the upper end of the left kidney, and extends upward between the peritoneum and the muscular tissue of the diaphragm. On the right side pus may pass between the layers of the lateral and coronary ligaments, thence to the falciform ligament, and may go even as far as the umbilicus. On the left side, infection originating in the cellular tissue about the upper pole of the kidney may dissect upward between the peritoneum and the diaphragm, or it may extend downward behind the colon.

The upper limit of the four intraperitoneal pouches is the under surface of the diaphragm; and, in the presence of infection, the viscera of the upper abdomen adhere to each other and to the abdominal wall, and form the lower limits of these spaces.

The right anterior intraperitoneal space is bounded behind by

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the right lateral and coronary ligaments of the liver. It is bounded on the left by the falciform ligament; and below this space is the upper surface of the right lobe of the liver. The lower anterior limit of this division is often formed by adhesions between the margin of the liver and the anterior abdominal wall, though, if the infection arises below, the lower boundary is formed by adhesions between the colon, stomach, and omentum, to the anterior abdominal wall. If the appendix is the source of the trouble, and the infection comes in from behind, the line of adhesions will be at the anterior edges of the liver, omentum, and colon, with the pus cavity in front, pushing the liver down and back. This right anterior space communicates at its outer side with the subhepatic pouch, and, through this, with the lumbar pouch. Infection from the appendix may pass up through the lumbar and subhepatic pouches to the subphrenic; and infection from perforating ulcers may also pass downward through these pouches to the lower abdomen.

The left anterior intraperitoneal space is limited by the left lateral ligament and the diaphragm, and is bounded on the right by the falciform ligament and reflected portions of the peritoneum from the gastrohepatic and gastrosplenic ligaments. Below this space to the right is the stomach; below, to the left, the spleen and the left abdominal wall. An abscess in this space is often spoken of as a perigastric abscess or as a perisplenic abscess; and most of the infections in this space are the result of perforating ulcers of the lesser curvature of the stomach.

The right posterior intraperitoneal space or subhepatic pouch is bounded above and in front by the liver and gall-bladder; the right lateral and coronary ligaments are also above this pouch. Posteriorly are the right crus of the diaphragm and the right kidney. To the left of this space are the duodenum, the foramen of Winslow, and the vessels of the liver and the common bile-duct. This space communicates with the lesser peritoneal cavity through the foramen of Winslow; and the appendix is most often the source of infection.

The left posterior intraperitoneal space is the same as the lesser peritoneal cavity. It rests on the left crus of the diaphragm and on

the pancreas. To the left is the spleen. In front are the liver, lesser omentum, and posterior wall of the stomach. On the right is the duodenum, the foramen of Winslow, liver vessels, and the bile-ducts. This pouch is not so often the seat of infection as the other spaces. Infection extending directly to this fossa most often has its origin in perforating ulcers of the posterior wall of the stomach.

A detailed knowledge of the anatomic divisions and boundaries of these spaces is important, even though it is often difficult to determine clinically just which one or how many of these pouches contain infection. An abscess may invade any one of these spaces alone, or it may extend to several of them at the same time.

ETIOLOGY

Infection seldom, if ever, originates in these spaces. It is the general opinion that the infection most often arises in the appendix. I have never seen a case of primary subphrenic abscess. Provided the subhepatic pouch is classed as a subphrenic compartment, infections originating in the appendix are more likely to extend to this compartment. It has been contended that the largest percentage of these cases are secondary to perforations of the stomach and the duodenum. In reviewing our series of 36 cases, I found that the largest number were associated with former operations for appendicitis. In several instances, however, it was impossible to say whether or not the appendix was the source or cause of the infection. In many, the appendiceal operation had been performed months before; the relationship was therefore remote.

There can be no question but that the subphrenic abscess is often secondary to some focal infection, such as tonsillitis, influenza, boils, etc. The following cases are striking illustrations:

CASE A (98,059).—This patient, a man of twenty-two, had grip one month previous to coming to the clinic. He was in bed with fever for three days. Two weeks later he had a chill, which was followed by another within a few days. After that he had fever in the afternoon and occasional chills and vomiting. He complained of pain in the region of the right kidney, and had lost 30 pounds in weight. Leukocytes, 18,200. The roentgenogram

showed a raised diaphragm on the left side. On exploration, a subdiaphragmatic abscess in the left anterior intraperitoneal fossa was found. The pain in the region of the right kidney had been misleading. There were slight tenderness and possibly a little rigidity of the muscles on the same side. The infection in the subphrenic region, in this case, undoubtedly gained entrance through the circulation at the time the patient had the infection of the throat. General infection followed within a few days of the focal infection.

CASE A (100,797).—A man, aged twenty-three. Eight months before coming to our clinic he had had several carbuncles on the back of his neck, from which he recovered slowly. The last attack occurred three months previous, and one month previous he had a sudden colicky pain in the right lumbar region, with a temperature of 101°F. After that the pain and tenderness continued in the right subdiaphragmatic region, with a rise in temperature every day. At operation a right subdiaphragmatic abscess (posterior intraperitoneal), containing several ounces of pus, was drained.

The patient had been free from carbuncles for about a month, when pain occurred suddenly in the subphrenic region, but as no other source of infection could be found, I felt sure that the subdiaphragmatic abscess was secondary to the infection from the carbuncles.

CASE A (120,122).—A man, aged thirty-five. He had a subdiaphragmatic abscess following an extensive injury to the perineum seventeen months before he came to our clinic for examination. In the accident a large piece of steel had been driven through the perineum into the bladder. There was more or less general infection. A large abscess in the left loin was drained, which, I believe, was a subdiaphragmatic abscess caused by extension of the infection through the lymphatics from the perineum. At autopsy an abscess was found in the left posterior intraperitoneal pouch, with multiple abscesses in the liver. The infection could not be traced from the perineum to the subdiaphragmatic region, but, I think it is fair to assume, the subdiaphragmatic abscess was secondary to the infection following the injury.

A subphrenic abscess is frequently associated with general peritonitis. The Fowler position may be employed to avoid this complication. Barnard¹ called attention to the fact that, when a patient lies flat on his back in bed, the posterior extremity of the

subphrenic space is about one-half inch from the bed mattress. The pouch of Douglas, in the pelvis, is also about the same distance

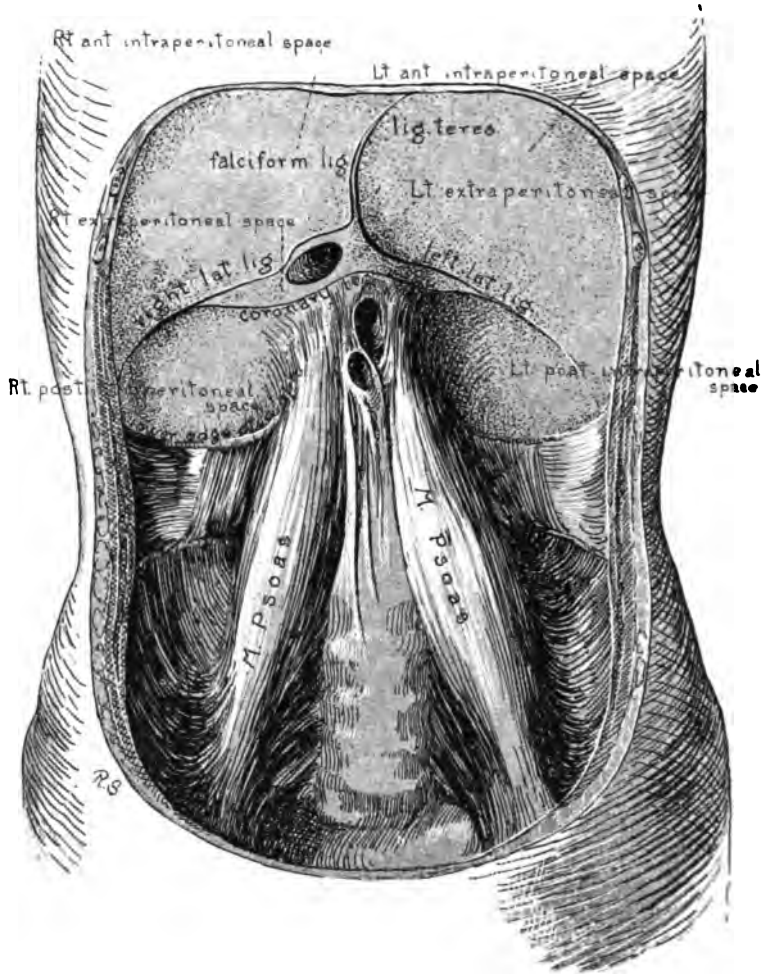


Fig. 105.—Diagram showing subdiaphragmatic spaces and boundaries formed by ligaments.

from the mattress. Between these two pouches is a bridge of thick muscle, kidneys, and perinephritic fat. Profuse serum is thrown out when the peritoneum is invaded, and this gravitates

into these pouches. If the patient is propped up on pillows when this fluid is still in the serum state, it all gravitates into the pelvic pouch, where it may be drained. Knowing that subdiaphragmatic infection is frequently associated with low-grade infections in the peritoneal cavity, I think it is well to be on the lookout for accumulations of pus in these pouches in septic patients who continue toxic.

Ross² reviewed 3391 consecutive cases of acute appendicitis, and among them found 30 subphrenic cases, or 8 per cent. of the acute appendiceal cases. He notes that of 500 children under fourteen years of age who had been operated on for appendicitis, there was only one case of subphrenic abscess. Ross says that by far the most frequent mode of infection of the subphrenic region is the direct extension up the peritoneal fossæ.

SYMPTOMS

The symptoms produced by these abscesses vary greatly; in many cases there is more or less of a general toxemia, with intermittent temperature, chills, and constant and marked leukocytosis; often the local symptoms do not appear until late. If the condition is the result of perforating ulcers, the previous history of ulcers will help in making the diagnosis. If it is the result of infection in the appendix, the symptoms will depend on the time the patient is seen. If the subphrenic abscess is present at the time of the operation on the appendix, it will usually be discovered. Undoubtedly, in some of these cases, in which the subphrenic infection is not a direct extension from the appendiceal infection, the subphrenic abscess has not been discovered at the time of the first operation.

Twenty-eight of our 36 patients were men. The ages varied from fourteen years to more than sixty years, though the greater number occurred between twenty-five and thirty-five years of age. The onset of the symptoms was usually slow, though in some cases it was sudden. The pain was pleuritic in character; respiration was painful. The onset may be insidious, with sepsis and a rise of temperature, as in a few of our cases in which there never were localized symptoms. In one case of continued sepsis the clinical

diagnosis of left subphrenic abscess was made on account of the raised and fixed diaphragm on that side. The leukocyte count is usually high. In 16 of our cases it varied from 8800 to 22,000; in only 3 was it normal, and in these the abscesses had evidently existed for some months. I believe that a high leukocyte count in uncertain conditions is always suggestive of a subphrenic abscess.

In our cases the duration of the trouble varied from three days to ten months. The roentgen ray was especially helpful in diagnosing four cases. In several the diagnosis was definitely established with the aspirating needle, and I believe the needle is a very important aid in locating these abscesses. The local symptoms of pain and tenderness may be marked. Frequently, the muscles of the loin are rigid. In the latter cases a mass can usually be palpated.

A subphrenic abscess is not infrequently associated with, or the result of, other infections in the peritoneal cavity. I wish to emphasize the importance of being on the lookout for these abscesses in connection with all types of septic conditions, no matter where the primary focus may be located. The cases in this series have been separated into nine groups according to the source of infection, as follows:

GROUP I (9 CASES).—SUBPHRENIC ABSCESSES ASSOCIATED WITH APPENDICITIS

Ages of Patients.—Fourteen, nineteen, twenty-three, twenty-four, twenty-six, twenty-eight, thirty-four, thirty-four years; men, 8; women, 1.

Blood.—Findings were noted in 7 of the 9 cases. All of the 7 had leukocytosis—8800 white blood-cells to 22,000 white blood-cells.

Roentgen Ray.—Not noted in 6 of the cases; negative in 1 case; high lying and fixation of the diaphragm in 2.

Duration of Trouble.—Three, four, eight, twelve, sixteen, twenty-four, and forty weeks.

Results.—Eight recovered sufficiently to return home; 1 died, aged twenty-three; necropsy showed multiple abscesses of the liver.

Symptoms.—Pain in the right side and in the back; rigidity of

muscles; tenderness; fever; chills; sweats; in some instances distinct masses; loss of weight; leukocytosis. (These symptoms usually developed following appendectomies or acute attacks of appendicitis.) Three cases developed shortly after appendectomy. One patient had an apparently normal appendix removed; infection of the wound followed; shortly afterward a kidney-stone was passed. Two cases apparently originated from ruptured appendices. In one there was drainage of a subdiaphragmatic abscess two months after drainage of an appendiceal abscess. One patient was operated on for appendicitis eight months previously, but the appendix was not found. The symptoms continued after the operation. One patient had an appendectomy nine years before coming for examination; the appendiceal stump was removed at operation in our clinic for drainage of the abscess.

GROUP II (7 CASES).—SUBDIAPHRAGMATIC ABSCESSES ASSOCIATED WITH GALL-BLADDER OPERATIONS

Ages of Patients.—Twenty-three, thirty-seven, thirty-nine, forty-two, forty-four, forty-six, forty-six years; men, 1; women, 6.

Blood.—Noted in one case only; leukocytosis, 15,000.

Duration of Trouble.—Eight, eleven, sixteen, seventeen, twenty, thirty, and one hundred twenty days after operation.

Results.—Three patients recovered sufficiently to return home; 4 died—1 in two months, 1 in fifteen days, and 1 in thirteen days, after operation, and 1 two weeks after drainage of an abscess that developed after the operation on the gall-bladder four months previously.

GROUP III (7 CASES).—SUBPHRENIC ABSCESSES ASSOCIATED WITH RUPTURED DUODENUM

Ages of Patients.—Thirty-one, thirty-four, thirty-six, fifty-one, fifty-nine, sixty, and sixty-three years, all men.

Blood.—Noted in 3 cases, and leukocytosis in all, varying from 10,000 to 21,000.

Roentgen Ray.—Not noted in 5 cases; negative in 2.

Duration of Acute Trouble.—One week; ten days; two, three, and three weeks; three and ten months.

Results.—Six patients recovered. One patient, aged fifty-one years, died eight days after operation; the necropsy showed double pleural pneumonia with degeneration of the liver. In nearly all cases there was a long history of duodenal ulcer with sudden acute pain (rupture); subsequent formation of tumor, fever, etc.

GROUP IV (4 CASES).—SUBPHRENIC ABSCESES ASSOCIATED WITH RUPTURED GALL-BLADDER

Ages of Patients.—Thirty-two, fifty-eight, sixty-four, and sixty-eight years; all men.

Blood.—Noted in 2 cases—6000 and 16,800. Not noted in 2 cases.

Roentgen Ray.—Not noted.

Duration of Trouble.—Ten days; two, six, and eight weeks.

Result.—All recovered.

Symptoms.—Usually acute, sudden, severe pain, following long gall-bladder history with tumor-formation around costal margin; rigid muscles; fever.

GROUP V (2 CASES).—SUBPHRENIC ABSCESES ASSOCIATED WITH PERFORATING GASTRIC ULCERS

Ages of Patients.—Thirty-six and fifty-eight years; both men.

Blood.—Not noted in 1 case; leukocytosis, 16,000 and 20,000.

Roentgen Ray.—Not noted.

Duration of Trouble.—Four and nine months.

The patient was drained at the time of the rupture, but the abscess reformed.

Results.—One patient recovered; 1 died (abscess ruptured through the pleura and emptied into the bronchial tube).

Symptoms.—Usually a history of gastric ulcer and acute pain at the time of the rupture, followed by localized mass in the epigastric region.

GROUP VI (1 CASE).—SUBDIAPHRAGMATIC ABSCESS FOLLOWING OPERATION ON THE STOMACH

Age of Patient.—Fifty-one years; man. Operation for cancer of the stomach. One-half of the stomach was resected and gastro-enterostomy was made. The patient developed pneumonia in five days and died twelve days after the operation. The necropsy showed pneumonia involving the lower lobes of both lungs and subdiaphragmatic abscess, the result of necrosis along the suture line of the gastro-enterostomy.

GROUP VII (1 CASE).—SUBDIAPHRAGMATIC ABSCESS ASSOCIATED WITH GENERAL PERITONITIS

Age of Patient.—Fifty-four years; woman.

Blood.—Not noted.

Roentgen Ray.—Not noted.

Result.—Died three days after subtotal abdominal hysterectomy and appendectomy.

Necropsy.—Right empyema; subdiaphragmatic abscess over liver, right side; general peritonitis; intestinal paresis; sepsis following the operation.

GROUP VIII (2 CASES).—SUBPHRENIC ABSCESS ASSOCIATED WITH TUBERCULOUS LESION ELSEWHERE IN ABDOMEN

Ages of Patients.—Thirty-three and fifty-six years; both men.

Blood.—No leukocytosis in either case.

Roentgen Ray.—Negative in 1 case; no record in 1 case.

Duration of Trouble.—Four and ten months.

Results.—Both patients recovered.

Symptoms.—In 1 case pain, fever, and loss of weight for four months; rigid muscles and increased liver dullness. In the other case the symptoms resembled those of ruptured gall-bladder.

GROUP IX (3 CASES).—SUBPHRENIC ABSCESS FOLLOWING FOCAL INFECTION

Ages of Patients.—Twenty-two, twenty-three, and thirty-five years; all men.

Blood.—Leukocytosis in all three cases, varying from 18,000 to 22,000.

Roentgen Ray.—Fixation of diaphragm with elevation in 2 cases; negative in 1 case.

Duration of Trouble.—Six, four, and two weeks.

Results.—Two died from general sepsis and multiple abscesses of the liver; 1 recovered.

Symptoms.—In 1 case the trouble apparently followed an attack of grip one month previously; chills, fever, pain over the left kidney, with mass in the left side and rigidity; rapid loss of weight. One case apparently followed multiple carbuncles, with sudden pain in the right lumbar region and fever. One case followed drainage of an abscess in the loin and suprapubic cystostomy done six weeks previously, with fever, pain, etc., after operation.

TREATMENT

The treatment consists of free drainage as soon as the diagnosis has been established. The operator should plan an incision which will offer the most direct access to the abscess cavity. More often this will be posterior, and the dissection will extend upward. At

times it will be necessary to drain through the pleura; and then it will be best carefully to suture the intercostal muscles to the diaphragm before opening the abscess, or to pack gauze down through the pleura to the unopened abscess, and leave it in place for several days to form protective adhesions before opening the pus cavity, shutting off, in this way, the pleural cavity from infection. When the abscess is opened, there will usually be a gush of a large quantity of pus, and a good-sized cavity will remain. If the drainage-tubes are removed too soon, the opening will close over, and the pus will again accumulate, requiring secondary drainage. I believe these abscess cavities, especially if the abscesses are of long standing, should be treated in much the same way as empyema cavity is treated; and the drainage-tubes should be kept in place for a considerable period. The surrounding viscera having been displaced for some time become firmly fixed in their new position; and it requires more than a few days for the space to become obliterated. For this reason I often have these patients wear a tube-drain for several weeks, or at least until the tissues have had time to obliterate the space formerly occupied by the abscess.

The subphrenic abscess is attended with considerable mortality. The unfortunate results are often due to the fact that the condition was not diagnosed until the infection had become too extensive to be relieved by drainage.

In our series of 36 patients there were 11 deaths. In almost every instance death was due to an extension of the infection to the liver and to the formation of multiple abscesses in this organ. From a review of these cases it seems to me that better results will be attained—(1) By efforts to make earlier diagnoses; (2) by being suspicious of any case that shows more sepsis than can be accounted for, and (3) by employing the aspirating needle early. When drainage has been established, it is important to maintain it until the infection has all disappeared and until there has been ample time for the cavity to become obliterated.

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UROGENITAL ORGANS

PERINEPHRITIC ABSCESES *

WILLIAM F. BRAASCH

While the subject of perinephritic abscess has been well reviewed in various articles, its exact pathology is still undetermined, and the question as to whether a perinephritic abscess may originate in the perirenal tissues without any primary involvement remains unanswered. Perinephritic abscesses have been referred to as primary or secondary: those originating in the perinephritic tissues being termed primary, while all others, whether originating in the kidney or some other focus, have been regarded as secondary. The existence of a primary perinephritic infection has never been definitely established either at operation or at autopsy. Because of the large amount of evidence which demonstrates that infection of the perirenal tissues is secondary to infection in surrounding foci, it would be more logical to regard all perinephritic infection as secondary or metastatic. A division may be made between an abscess of renal origin and one arising in other tissues. The former group should be termed true perinephritic abscess; the latter, subdiaphragmatic or retroperitoneal.

A review of the cases operated on in the Mayo Clinic for abscess in the perinephritic tissues lends support to such classification. One hundred and one patients had been operated on up to January 1, 1914, for abscess involving the perirenal area. In 34 of this number it was proved at operation that the abscesses were secondary to lesions in the extra-urinary tissues, and because of their situation they were termed subdiaphragmatic or retroperitoneal

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abscesses. This group has been considered separately in a recent paper by Judd.¹ There remain for consideration 67 with lesions which may be regarded as perinephritic abscess. Of this number, 46 were male and 21 female, or practically a ratio of 2 to 1. In 36 patients the abscess was found on the right side, and in 31 on the left, or practically equal. On reviewing the cases the following direct etiologic factors were found in the order of their frequency.

1. Pyonephrosis.
2. Renal tuberculosis.
3. Nephrolithiasis.
4. Cortical abscess.
5. Traumatic rupture.

Pyonephrosis.—Inflammatory or mechanical destruction of the renal tissue may exist for years without seriously incapacitating the patient except by occasional attacks of pain. A perinephritic abscess will not infrequently suddenly complicate the situation, and the patient is then forced to seek surgical relief. The abscess is usually drained at once, and the patient may go about for years with a discharging sinus unless the kidney is removed. Pyonephrosis was found as the source of perinephritic abscess in 12, or 19 per cent., of the 67 cases. Of this number, 3 were large infected hydronephroses of long standing. Immediate nephrectomy was done in 10 cases, and drainage with subsequent nephrectomy was done in 2. The value of cystoscopic examination is rendered apparent in that the nature of the lesion and the functional destruction of the kidney were determined prior to operation. Drainage alone in these renal lesions is frequently attended with various complications, and subsequent nephrectomy may be rendered difficult.

Renal Tuberculosis.—Renal tuberculosis as the apparent etiologic factor of perinephritic abscess was present in 10, or 15 per cent., of the cases. Evidence of perirenal infection with renal tuberculosis is often found at operation and, while it is more often characterized by the sclerotic type, the formation of abscess may occur. Severe pain occurring with renal tuberculosis may be the result of mechanical obstruction in the ureter and is usually

transitory in character. With perinephritic complications the pain more often remains continuous over a period of weeks. It is not usually so acute as with other types of perirenal abscess, nor are the other symptoms so marked, the temperature and the leukocyte count being considerably lower. The prognosis of perinephritic abscess accompanying renal tuberculosis is less favorable than with other forms of perirenal infection. Of the 10 cases operated on, six died within a few months after operation. In seeking the cause of the development of perinephritic abscess with renal tuberculosis it may be inferred that it is the result of secondary mixed infection. In three cases, however, no bacterial growth was reported on culture.

Nephrolithiasis.—With stone in the kidney or ureter the pain is usually intermittent in character. When the pain persists over a period of several days or weeks, it is the result either of continuous urinary obstruction or of perinephritic abscess. The perinephritic abscess frequently brings the patient suffering from nephrolithiasis to a surgeon, when the occasional colic will not. Nephrolithiasis was the direct cause of perinephritic abscess in 11, or 16.4 per cent., of our cases. In each there was a cortical abscess, the evident result of the stone, which in turn was the evident cause of the perinephritic infection. The appearance of the perinephritic abscess was usually marked by a continuous severe pain persisting for several days or weeks. In a number of cases, however, there had been no recent clinical data suggestive of any complication. The abscesses in these cases were small and had burrowed into the perirenal fat. Nephrectomy was performed in six cases, while nephrolithotomy and drainage of the perinephritic abscess effected a cure in the other five cases. It is an interesting fact that the cases in which the perinephritic abscess was directly connected with a cortical abscess healed merely by draining the perinephritic abscess. This apparently explains why drainage of the perinephritic abscess may suffice to cure the condition, even though a cortical abscess be the underlying cause.

Cortical Abscess.—Direct evidence of acute localized renal infection, other than with pyonephrosis, lithiasis, or tuberculosis, as an

etiologic factor in perinephritic abscess was found in 12, or 18 per cent., of the cases. Pus in varying amounts was found in the urine in all save two. Eight of the patients were subjected to cystoscopic examination, and the urine catheterized from the affected kidney showed microscopic evidence of infection. Of considerable interest are the two cases in which repeated analysis of the urine failed to show any marked pathologic element save a trace of albumin and a few hyaline casts that were regarded as of no practical significance. At operation, perinephritic abscesses were found in direct communication with single small cortical abscesses. Recovery of the patients followed simple drainage. In four patients but a single cortical focus could be ascertained at operation; three of these recovered after drainage; the fourth suffered from a recurring abscess a month later. In two cases multiple cortical abscesses were found and nephrectomy was performed. The clinical symptoms in this group were characterized by their severity, evidence of marked infection being present in all. The leukocyte count was high and varied from 15,000 to 34,000.

In the discussion of this group of cases it is of interest that none of our series of perinephritic abscesses was found to have originated from a primary pyelitis or pyelonephritis. In the 211 cases of pyelonephritis and pyelitis which have come under our observation, there is no record of previous perinephritic abscesses. Chronic pyelonephritis or pyelitis is therefore an infrequent cause of acute perinephritic infection.

Traumatic Perinephritis.—Perinephritic abscess may complicate traumatic rupture of the kidney, usually from one to three weeks following the injury. It occasionally follows severe injury to the loin, even when there is no clinical evidence of renal rupture. Albarran's well-known experiment demonstrated that perinephritic abscess may be caused by trauma directed to the perirenal area. It might be inferred, however, that perinephritic abscess following such injury may result from a rupture of the kidney too slight to give clinical evidence. It is well known that the kidney may be ruptured with a slight injury only. It is not impossible that the source of many perinephritic

abscesses following injury to an affected loin is a superficial rupture of the kidney with secondary infection. Perinephritic abscess complicating rupture of the kidney was found in four, or six per cent., of our series. In three cases nephrectomy was necessary; in one case in which an abscess followed rupture of an upper pole, drainage alone was done, the patient making an uneventful recovery.

Perinephritic Abscess Without Renal Involvement.—There remain 18 patients in whom no evidence of renal involvement was ascertained on clinical examinations. Two of this group had symptoms suggestive of possible spinal involvement and one later developed a typical psoas abscess. Another patient gave some evidence of possible pelvic source of infection, which leaves 14, or 21 per cent., of patients with no data as to the source of the infection. In many of this group the more recent methods of examination were not employed. Doubtless, with the aid of these methods, some evidence of renal involvement would have been found in a considerable percentage of these cases. There will be, however, a small group of cases in which no evidence of renal infection is found on clinical examination, and the etiology of which may not be ascertained at operation because of the exigencies of the case. This type of perinephritic abscess is usually more acute, and in all probability forms a comparatively large proportion of the perinephritic abscesses seen in the emergency hospitals of large cities. It would seem logical to infer that a small solitary cortical or subcapsular abscess is the cause of these unidentified perinephritic abscesses. The frequency with which hematogenous infection subsequent to some superficial lesion occurs in cases of both renal and perirenal infection would suggest their close relationship. It is this small proportion of perinephritic abscesses which has been regarded as primary, because the evidence of renal involvement ascertained by means of the data available at operation was necessarily incomplete. It is in recent years only that the importance of several methods of clinical examination has been realized in the diagnosis of perinephritic abscess. With the aid of these methods, the renal origin of such abscesses will be found more frequently. The diag-

nosis of perinephritic abscess would be inexact without the data obtained through the following methods:

1. Repeated urinalysis.
2. Bacteriologic investigation of the urine catheterized from each kidney.
3. Estimation of the comparative renal function.
4. Radiologic examination, including that of the urinary tract and of the thorax.
5. Pyelography.

Urinalysis.—Israel² has called our attention to the value of repeated examinations of the urinary sediment in determining the renal origin of perinephritic abscess. He maintained that a few red blood-cells and pus-cells, together with albumin and occasional casts, may be found after repeated examination in practically every case of perinephritic abscess. On the other hand, it must be remembered that a few red blood-cells and pus-cells may be found in the urine as the result of a coincidental lesion existing in the lower urinary tract, a fact which lessens their diagnostic value. The absence of red and white blood-cells in the urine would not necessarily exclude the possibility of renal origin. A practically negative urinalysis was reported in 10 of the 14 cases of unidentified perinephritic abscess. In a number of these, however, but one urinalysis was made. On the other hand, in the series of 34 cases of subdiaphragmatic abscesses of definite extrarenal origin reported by Judd,¹ red blood-cells or pus-cells were found in the urine in three, the origin of these cells being in all probability in coincidental chronic urethritis, trigonitis, or prostatitis which might be difficult to determine clinically.

Bacteriologic Examination.—Baum³ reported seven cases of perinephritic abscess in all but one of which there were staphylococci in the urine. Although it has been demonstrated that bacteria, and particularly staphylococci, may pass through the kidney and be found in the urine without the existence of any renal lesion, the proportion of such cases is very small. Baum's report is one of exceptional interest and suggests a method which should be of considerable value in determining the renal origin of perine-

phritic abscess otherwise overlooked. The accuracy of this report is corroborated by numerous control tests, and by one case in particular, in which the same organism was obtained from the urine as appeared in the perinephritic tissue. We have tried the method in six cases, in four of which staphylococci were found in the urine; in two cases the urine was negative on culture, and in one of these a retroperitoneal abscess extending from a perforated duodenal ulcer to the perirenal region was found at operation. In two cases a differential culture of the urine catheterized directly from the kidneys showed staphylococci from the affected side only.

Renal Functional Test.—If a renal lesion is the cause of perinephritic abscess, a comparative diminution of functional activity from the affected kidney must follow. Although the cortical lesion may be slight, an appreciable difference should be noted between the functional output of the two kidneys. Using phenolsulphonephthalein, which lends itself admirably for this purpose, we have demonstrated a well-marked diminution of dye return from the affected side in five cases. (This number includes three cases reported in a previous article.⁴) In one of these the microscopic examination of the urine was practically negative save for a trace of albumin. In a case of retroperitoneal abscess involving the perirenal area and secondary to duodenal ulcer, no difference in the functional activity of the two kidneys was found. In one case of chronic perinephritic abscess of probable renal origin the difference was too slight to be of practical value.

Radiographic Evidence.—Roentgen examination of the urinary tract must necessarily be a preliminary step in every case of perinephritic abscess. It must be emphasized that a well-marked etiologic lithiasis may be present without causing preliminary subjective symptoms. Roentgen examination of the lower thorax, made in order to observe any abnormal change in the position of the diaphragm, may be of considerable practical value in differential diagnosis. This is particularly true on the left side, where both a perinephritic and a subdiaphragmatic abscess may be the cause of considerable displacement.

Pyelogram.—Renal infection, past or present, usually leaves

some evidence of its presence in the outline of the pelvis or ureter which can be rendered visible by means of the pyelogram. Very recent infection may not, however, cause sufficient change in the pelvic outline to be of diagnostic value. The pyelogram was of considerable value in two of our cases in which the clinical data suggestive of renal involvement were indefinite.

Differential Diagnosis.—It may be difficult on clinical examination to differentiate perinephritic abscess from acute septic nephritis. In the early stages of abscess development the symptoms of the two conditions may be quite similar; both may be characterized by high temperature, leukocytosis, severe pain, and tenderness referred to the affected kidney area. However, with the increase in size of the perinephritic abscess, palpation will usually determine the condition. Although the existence of an acute perinephritic abscess may easily be determined, chronic perinephritic abscess may remain unrecognized until revealed at operation.

It may be difficult to differentiate between a subdiaphragmatic or retroperitoneal abscess and true perinephritic abscess. As a rule, symptoms of the original lesion and a more general invasion of the tissues will differentiate the three conditions. The data obtained through urinalysis, cystoscopic examination, bacteriologic examination, renal functional tests, and the roentgenogram are often of considerable aid in differentiation.

Results.—Of the 67 patients operated on at the Mayo Clinic, two (3 per cent.) died as the result of the operation. Three other patients were reported dead at three, seven, and twelve months, respectively, after operation.

The subsequent course was ascertained in 51 of the remaining patients. In 18 of this number the wound had healed in less than a month after operation. Of the remaining patients, 16 continued to drain for two months, 6 drained for three months, and 3 drained as long as six months after operation. The fistula persists to the present date in 4 patients, all of whom drained longer than six months. In 2 of these patients an etiologic renal lesion was ascertained at the time of drainage and subsequently nephrectomy was

advised. In the other 2 no evidence of renal lesion was discovered on clinical examination; however, the more recent clinical tests were not employed. One of these patients, drained one and one-half years ago, has returned with cystoscopic evidence of an etiologic renal lesion not previously discovered.

The question is frequently raised at operation whether immediate nephrectomy or drainage of the abscess alone is indicated. In the presence of a large fluctuating abscess and marked physical weakness drainage will suffice; if, however, evidence of considerable renal involvement has been ascertained, immediate nephrectomy as well as drainage is to be preferred when possible. The practical importance of previously ascertaining the underlying renal condition is self-evident.

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SIGNIFICANCE OF VESICAL SYMPTOMS IN THE DIAGNOSIS OF RENAL CONDITIONS *

WILLIAM F. BRAASCH

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The relation of vesical symptoms to renal disease is much the same as that of gastric symptoms to disease in the gall-bladder, appendix, or duodenum. It is now generally recognized that reflex gastric symptoms may predominate in the clinical picture as the result of disease in the adjacent alimentary tract. The underlying lesion in the kidney may have little or no localizing symptoms, while the secondary vesical condition may give rise to all the subjective symptoms. The renal conditions which are most frequently the cause of vesical symptoms are: (1) Tuberculosis; (2) pyelonephritis; (3) lithiasis.

1. RENAL TUBERCULOSIS.—Although the fact that vesical symptoms usually predominate with renal tuberculosis has been reiterated by many observers, it is unfortunately true that it fails to obtain general recognition. Of the 203 cases of renal tuberculosis which I reported several years ago,¹ 90 per cent. of the patients had vesical symptoms extending over a period of six months and more than 50 per cent. more than a year. The remainder had vesical symptoms the cause of which remained unrecognized in some instances as long as ten years. During all of this time the vesical symptoms were treated by means of lavage of the bladder and various internal medications. It will be a conservative attitude to regard all cases of persistent irritability of the bladder with pyuria, particularly when in the young adult, as due to renal

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tuberculosis until the contrary can be proved. Early recognition of the disease not alone improves the prognosis, but, of equal importance, it may prevent the unfortunate deep-seated infection of the bladder which is so difficult to eradicate. As a rule, the vesical symptoms with renal tuberculosis are more severe in the male patient than in the female. A well-advanced renal tuberculosis with comparatively slight irritability of the bladder occurs more frequently in the female than in the male. In keeping with the comparative irritability of the bladder is the fact that hematuria with renal tuberculosis also occurs more often in the male. Most of the hematuria noted by patients arises from the inflamed and ulcerated mucosa of the bladder. Gross hematuria originating in the tuberculous kidney usually appears in large amounts, and occasionally occurs before any vesical irritability has developed.

2. PYELONEPHRITIS.—Diffuse infection of the renal parenchyma and pelvis with organisms other than tubercle bacilli, and which come under the term of pyelonephritis, usually cause a variable degree of infection of the bladder. The resulting cystitis is usually less severe than that which occurs with tuberculosis, and consequently the vesical symptoms are less marked. Occasionally, however, the cystitis with a pyelitis may be marked, and when accompanied by areas of ulceration, is suggestive of tuberculosis. When the infection is unilateral and the urine from the affected side is grossly purulent, the two conditions may closely resemble each other. If guinea-pig inoculation is impracticable, error in diagnosis may easily occur. On the other hand, general infection of the kidney is often present, with purulent urine but with little or no infection of the bladder or vesical symptoms. Localizing symptoms referred to the kidney occur even less frequently with pyelonephritis than with renal tuberculosis, the irritability of the bladder alone calling attention to the presence of the pyelonephritis. Pyelonephritis as the cause of cystitis in the adult male was found in 109 of the 121 cases recently reported from the Mayo Clinic.² In the adult female the proportion of the cases of cystitis as the result of chronic renal infection, although much lower than in the male, is nevertheless very great. No case of so-called cystitis

should be regarded as such without a careful exclusion of possible renal infection. The treatment of such cystitis by means of internal medication supposed to have a urinary antiseptic or antispasmodic action, or, still worse, operations on the pelvic organs, is to be strongly condemned unless a careful investigation has first been made to rule out the presence of an etiologic renal infection. The simplest way to establish the presence of renal infection obviously is by ascertaining the presence of pus in the urine catheterized from the respective kidneys. The amount of pus in the urine thus obtained varies markedly, depending on the degree of infection at the time of examination. The activity of a chronic renal infectious process varies to a considerable extent and at times may be practically dormant. Should the urine be catheterized during the interval of comparative improvement, only an occasional pus-cell might be found in the urine. Negative urine on a single renal catheterization would therefore not exclude the possibility of a quiescent renal infection. To exclude the renal infection definitely a bacteriologic examination of the urine would be necessary, and only if negative might be regarded as absolute evidence. A pyelogram in doubtful cases may also be of considerable value. It has been demonstrated that infection in the renal pelvis and ureter is followed by dilatation in their walls as the evident result of cicatricial change. Demonstration of such dilatation in the outline of the renal pelvis or ureter would be conclusive evidence of previous active infection, even though the urine failed to show any evidence of active infection on microscopic examination. A pyelogram, moreover, may be of value in the differentiation between infection involving largely the pelvis and that involving the parenchyma, as ascertained by the changes peculiar to each other. Renal functional tests and phenolsulphonephthalein in particular, owing to its practicability, may be of corroboratory and differential value. It has long been known that diminution in renal destruction may frequently be ascertained by the degree of diminution of dye return. As Geraghty³ has shown, a pyelonephritis is characterized by considerable decrease in phenolsulphonephthalein return, while there is but little with pyelitis. Occa-

sionally, however, pyelonephritis may be present without any appreciable difference in functional output.

3. **LITHIASIS.**—At the time of colic resulting from urinary obstruction by stone in the kidney or ureter, irritability of the bladder and frequency of urination are often predominant symptoms and may be of importance in the differential diagnosis; in fact, the absence of vesical irritability coincident with pain would be a factor in exclusion in the interpretation of a doubtful renal or ureteral shadow. When the stone is lodged in the vesical portion of the ureter, and the pain is localized largely to the bladder and adjacent area, vesical irritation may be persistent. When the pain with low ureteral stone is localized to the suprapubic or low inguinal area, it is usually the result of a localized periureteritis. The impacted stone causes ulceration in the ureteral mucosa, and the resultant inflammatory reaction is the origin of constant pain. The radiation of pain with renal lithiasis may be largely referred to the area of the bladder. This is particularly true in children. Recently a little girl of ten came under my observation with symptoms only of severe sudden pain lasting a few minutes, localized entirely to the suprapubic area. In keeping with our policy to radiograph the entire urinary tract in cases of doubtful abdominal pain, her radiogram showed a definite stone in the right kidney, which was removed with her recovery.

CYSTITIS.—Although a very large proportion of cases of cystitis are the result of renal infection, it should not be stated that cystitis may not exist as a primary and sole focus of infection in the urinary tract. I have observed a number of cases of cystitis where careful examination of the urine catheterized from the kidneys, including bacteriologic tests, failed to show any evidence of renal infection. Such cases are less common in the male without urinary obstruction, but are of frequent occurrence in the female. The possibility of an easy route for ascending infection in the female may be an etiologic factor.

NEUROSIS OF THE BLADDER.—While such a term may not be clinically justifiable, it is often used to describe a condition of vesical irritability when after every method of modern diagnosis has been exhausted no apparent cause is demonstrated. Such a con-

dition of the bladder usually occurs when other evidence of neurosis is also present and appears to be part of a syndrome. It is this unfortunate group of patients who, in their effort to obtain relief for their vesical symptoms, are frequently subjected to repeated needless operations on the adjacent pelvic organs.

**SYMPTOMS OF THE BLADDER AS THE RESULT OF THE EXTRA-
VESICAL CAUSE.**—In the differential diagnosis of the various causes of irritation of the bladder, the influence of adjacent extravescical conditions should be considered. Although in a small proportion of cases the direct influence of extravescical conditions may be the cause of vesical symptoms, their importance has been greatly exaggerated. This is particularly true in displacement of a uterus, otherwise normal, and other conditions of the female pelvis. That operative interference is frequently employed for this condition is demonstrated by the long list of women suffering from vesical symptoms who have had repeated operations for uterine displacement, cystocele, etc., without improvement of these symptoms. The fact that countless women have marked displacement of the uterus without any vesical symptoms does not seem to be recognized. It is questionable whether displacement of the otherwise normal uterus can cause irritation of the bladder without a secondary complication.

When vesical symptoms do result from extravescical cause, they are the result of: (1) Pressure of a tumor; (2) mechanical interference; (3) malignant involvement, and (4) direct extension of an adjacent inflammatory process.

1. *Pressure of a Tumor.*—The pressure on the bladder of large tumors of extravescical organs may be the cause of vesical irritation. It is surprising, however, how small a proportion of uterine tumors, even though large, will cause irritation. Removal of a large uterus without tumor involvement in order to relieve vesical symptoms is seldom advisable. The following case may be cited as an illustration of a possible result from such erroneous interference:

M. G., female, aged thirty-two years; married four years, one child, aged three years. Soon after the birth of the child she complained of persistent irritability of the bladder and diurnal fre-

quency, which increased in severity. A year later, after a pelvic examination by her local surgeon, she was informed that the uterus was abnormally large and situated so as to press on the bladder and cause the symptoms. He advised hysterectomy, which was done. Her symptoms persisting, a year later she presented herself at our clinic. Cystoscopic examination and urinalysis revealed tuberculosis in the right kidney, with a moderate degree of cystitis. After the removal of the kidney, the patient's vesical symptoms rapidly improved and a year later were reported cured.

2. *Mechanical Interference.*—Mechanical obstruction to the urinary flow as the result of uterine displacement in an otherwise normal uterus is not common. Large tumors of the uterus and adnexa are only occasionally situated so as to cause mechanical obstruction to the urinary drainage. Cystocele, even though extensive, only in exceptional instances is the cause of actual urinary retention. Although marked uterine prolapse may be the cause of urinary retention more frequently than any other pelvic condition, it occurs in but a small proportion of the cases.

3. *Malignant Involvement.*—Involvement of the bladder by malignant conditions in the pelvic organs occurs less frequently than one might expect. The number of cases of cancer of the uterus with actual vesical involvement which may be visible on cystoscopic examination is surprisingly small. Cancer of the rectum involves the bladder more frequently than pelvic cancer. With a history of irritability of the bladder associated with rectal cancer a cystoscopic examination is always indicated.

4. *Inflammatory Extension.*—Vesical symptoms may result when the bladder becomes involved with an inflammatory condition in the female pelvis. Cystoscopic examination then shows either a punctate erosion or a bullous edema in that portion of the vesical mucosa adjacent to the inflammatory process. It is more apt to occur with acute inflammatory conditions and often subsides with the disappearance of the acute symptoms. Nevertheless, considering the wide-spread existence of pelvic inflammation, the number of cases in which the bladder is actually involved must be comparatively small.

In conclusion, therefore, I would urge a careful consideration of all the possible causes of vesical symptoms, including renal infections, ascending infection, local infections, ulceration, and neurosis, and that plastic operations on the pelvic organs be resorted to in only exceptional instances.

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STONES IN THE URETER *

WILLIAM F. BRAASCH AND ALEXANDER B. MOORE

Of the 742 cases of lithiasis of renal origin operated on at the Mayo Clinic up to June 1, 1915, 512 stones were removed from the kidney and 230 were found lodged in some portion of the ureter. To this number should be added 64 cases in which a stone lodged in the ureter was either removed at the time of the cystoscopic manipulation or was passed immediately after, making a total of 294 cases of stone in the ureter for consideration. It is our purpose to review a few of the various clinical data involving their diagnosis.

Localization of Pain.—Pain as a result of stone in the ureter occurs from two conditions, namely: (1) Because of intrarenal tension as a result of urinary obstruction, and (2) because of localized infectious changes.

A review of the localization of pain in our series of cases is of interest. Pain was referred largely to the renal area in 197 (67 per cent.) of the cases; to the upper abdominal quadrant in 45 (15 per cent.) of the cases; to the region of the lower ureter in 28 (9 per cent.) of the cases; and to the suprapubic area in 3 cases. No definite radiation of pain was reported in 16 cases and no pain whatever in 5 cases. It is obvious, therefore, that either an exploratory incision over the renal area or a roentgenogram of the renal area alone would fail to disclose the actual lesion. It is probably true that renal colic as a result of lithiasis is caused more frequently by stone lodged in the ureter than in the kidney. In a large number of cases in which the pain was referred to the upper abdominal quadrant it is easy to see how confusion with lesions in the upper

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abdomen might follow. In fact, in a number of cases the radiation of pain was so typical of disease in the gall-bladder that in the absence of urinary findings surgical exploration of the gall-bladder would have been justifiable without a preliminary roentgenographic examination. Of particular interest is the localization of the pain referred to the area of the lower ureter. It is probable that this group of cases is most frequently confused with appendicitis, particularly when the pain is on the right side. The localization may be so suggestive of appendicitis that, in case the urinalysis was negative, an exploration of the appendix might be justifiable without preliminary roentgenographic examination. The localization of pain to the region of the lower abdominal quadrant occurs usually as a result of ulcerative changes in the ureteral wall and subsequent peri-ureteritis. A history, therefore, of previous colic referred to the renal area with subsequent pain localized to the lower ureteral quadrant would be suggestive of an impacted ureteral stone with periureteritis. This would be particularly true if the pain, previously periodic, became continuous over a period of a week or more. It should be noted that there was a considerable number of patients who did not complain of definite radiation and a few who did not have attacks of severe pain. These patients came to operation either because of a consequent renal infection, urinary symptoms, or indefinite abdominal symptoms. It is undoubtedly true that stone in the ureter may exist for a long time, even a year or more, without being the cause of pain. Mechanical irritation caused by the stone itself will seldom produce pain. Occasionally, however, a history is obtained in which the patient claims to have been able to feel the stone in its passage from the kidney to the bladder, which in all probability is the result of a lesion in the mucosa subsequent to the passage of the stone. Eight patients gave a history of radiation of general abdominal pain, without localization, and with symptoms of vomiting and intestinal spasm suggestive of intestinal obstruction. Of this number, 3 had previously been operated on elsewhere for intestinal obstruction. This peculiar radiation of pain, together with secondary intestinal symptoms, is evidently due to reflex action of the sympathetic

intestinal nervous system. In 12 cases the degree of pain was secondary in importance to symptoms of gastric disturbance. The patients complained more of general nausea, epigastric distress, and indigestion than of the pain referred to the urinary tract. Such reflex disturbances are in keeping with the secondary symptoms observed with lesions in other extragastric conditions.

Occurrence of Vesical Irritability.—Vesical irritability was reported in 218 patients (74 per cent.). This condition occurs so frequently that its absence is of distinct value in differential diagnosis. Although it more often occurs only at the time of the pain, it may continue for a day or two following. Occasionally it may be persistent over longer periods and may be the predominant symptom. This is particularly true when the stone is lodged in the vesical portion of the ureter. When the stone bulges into the meatus it may in fact be considered a vesical stone so far as its effect on the bladder is concerned.

The Value of Urinalysis.—The practical value of the presence of a few red blood-cells or pus-cells in the urine in the diagnosis of ureteral stone has been exaggerated. Similar microscopic elements are found so frequently in the urinary sediment with slight lesions in the lower urinary tract that its diagnostic value is greatly lessened. The presence of a few red blood-cells or pus-cells in the urine, however, necessitates a careful roentgenographic examination of the urinary tract even though the subjective symptoms are of negative value. On the other hand, the absence of pus or red blood-cells would not exclude the possibility of stone in the ureter. Whereas catheterization of the ureter may localize the origin of the pus-cells, because of the possibility of traumatic hemorrhage it is of no value in localizing a few red blood-cells. Neither pus nor red blood-cells were found in 35 (12 per cent.) of the cases. An occasional red blood-cell only was found in 26 (9 per cent.) of the cases. An occasional pus-cell only was found in 7 cases. Both red blood-cells and pus-cells to a varying degree were present in the remaining cases.

Gross hematuria was reported in 41 (14 per cent.) cases of stone in the ureter, while with renal stone it was found in 56 per cent. of a

series of cases of renal lithiasis previously reported.¹ It should, therefore, be regarded as a symptom of less importance with ureteral stone than with renal stone. Persistent bleeding with stone in the ureter occurred in 7 cases and was the result of ulceration in the ureteral wall. In one case the stone had caused necrosis of adjacent blood-vessels with considerable resultant hemorrhage.

Palpation of the Stone.—Stone in the ureter is rarely palpable through the abdominal wall. We have observed one case, however, in which the stone could be rolled under the hand on deep pressure in the inguinal area. The stone on removal was four inches long and one inch in diameter. Our attention has recently been called to the value of palpation through the vagina or rectum in the case of stones lodged in the lower end of the ureter. Israel² claimed that he was able to feel the stone per vaginam and rectum in 39 per cent. of his cases. In the last 80 cases of stone in the lower ureter in which a special effort was made to feel the stone through the vagina or rectum it was definitely palpated in only 9 cases. Of these 80 cases, 48 occurred in the male and in only 3 cases could the stone be definitely felt through the rectum. This leads us to conclude that rectal palpation is only exceptionally of definite value in localizing stone. The various conditions simulating stone which may cause localized nodular change in the prostate, seminal vesicles, and ducts lessen the value of rectal palpation. In the 32 female patients the stone could be felt per vaginam in 7 (22 per cent.) cases. In a few other cases an area of thickening could be felt in the vault of the vagina, but was not definite enough to be of practical value. In order to be definitely felt per vaginam the stone should be at least a centimeter in diameter and should be situated within or immediately adjacent to the wall of the bladder. Unless so situated, stones of even several centimeters in diameter will not permit of palpation. It should be remembered that nodular changes in the lower ureter as the result of tuberculosis may occasionally simulate a stone. The fact that localized inflammatory areas of thickening may occur in the vaginal mucosa may also confuse the findings.

Treatment.—In the consideration of ureteral stone its renal origin should be borne in mind. In 41 patients a definite history was ascertained of one or more stones having been passed previous to the examination, and in 21 varying amounts of sand or fine gravel had been passed. Some of these gave a history of colic at intervals during a period of more than a year before passing their stone. The majority, however, passed the stone with the first attack of pain or with the second or third attack. In all probability the majority of stones in the ureter pass spontaneously, and for this reason surgical interference is seldom indicated with the first attack of pain. While no rule can be adopted, it would be rational, in the majority of cases, to wait at least two or three months until nature has made several attempts to dislodge the stone. On the other hand, repeated violent colic, the danger of renal destruction, and other complications as the result of an obstructing stone may necessitate its removal before this period has elapsed. Before an abdominal operation is attempted, the passage of the stone may be aided by the various methods offered by endoscopic technic, namely: (1) Catheter manipulation; (2) injection of sterile glycerin or oil; (3) fulguration; (4) ureteral dilatation; (5) cutting of the meatus, and (6) ureteral forceps. By means of these various methods we have been able to remove stone lodged in the ureter in 64 cases.

It has been claimed that the injection of oil and glycerin into the ureter would both increase the peristalsis and lubricate the walls of the ureter so that the stone would slide out. This theory, however, is not borne out by extensive observation. It is difficult to conceive how the natural efforts of peristalsis or how the natural lubrication in the ureteral mucosa could be improved on.

Forcible dilatation of the ureter below the stone by means of ureteral dilators may be of value, particularly if the position of the stone is altered in so doing. Not infrequently it is possible to grasp a small stone situated in the wall of the bladder by means of the ureteral forceps. Those well above the wall of the bladder, however, can be removed in this manner in exceptional cases only. Slitting the meatus and adjacent ureter may occasionally be indi-

cated with intramural stone. That no harm should follow the destruction of the ureterovesical valve has been demonstrated experimentally.³

It is our impression, however, that many of the stones lodged in the ureter which can be removed by means of these various methods will be passed spontaneously after dislodgement by means of the ureteral catheter. The stone becomes lodged in the ureter and subsequent colics may make its anchorage in the mucosa firmer. The passage of the ureteral catheter dislodges the stone, changes its axis, and the next colic forces it out. If this method should fail, an attempt should be made thoroughly to dilate the ureter below and, if possible, to grasp the stone with ureteral forceps. The use of the high-frequency current may occasionally be of value in disintegrating a small, fragile stone. It should not be forgotten, however, that change in the position of the stone as the result of such manipulation is fully as effective as that caused by ureteral catheterization.

Sources of Error in Diagnosis.—A greater percentage of error in the roentgenographic diagnosis of stone in the ureter will result from incorrect interpretation of a shadow than from failure to show it. Although there are a number of generally recognized data in regard to form, size, and density of the shadow which are regarded as characteristic of stone and of extra-ureteral bodies, respectively, such data cannot always be relied on. In fact, it is doubtful if an accurate diagnosis of stone in the ureter can be made from roentgenographic data alone in more than 60 per cent. of cases. The greatest percentage of error will probably occur in regarding extra-ureteral shadows, such as phleboliths, glands, etc., as explanatory of abdominal pain with subsequent negative exploration. Next in frequency will be the interpretation of stone shadows as caused by extra-ureteral conditions, and last in the list of diagnostic errors charged to roentgenography will be the stones that fail to cause a shadow in the roentgenogram. In our series the roentgenographic report was negative in 32 (11 per cent.) of the cases. The various causes to which the failure was ascribed are, in the order of frequency, as follows: (1) Error in roentgenographic

technic; (2) position of the stone; (3) size of the stone, and (4) the character of the stone.

1. Many various possible sources of error in roentgenographic technic make it practically impossible to make an ideal roentgenogram in every case in the course of routine roentgenography. There will always remain a few cases in which, if the preparation of the patient, the condition of the tube, and the condition and development of the plate had all been better, the stone-shadow, which was otherwise missed, might have shown.

2. It occasionally happens that the shadow of the pelvic bones obscures that of an overlying stone. Such error may be obviated by adjusting the angle of the ray so as to exclude the shadow of the pelvic bones. It is not always possible to do so, however, and in the course of routine roentgenography there will always remain an occasional stone which is overlooked because of the pelvic bone shadow.

3. The degree of obstruction is not dependent on the size of the stone. Not infrequently a very small stone, even as small as a pin, head, lodges in the ureter and causes inflammatory reaction in the adjacent ureteral mucosa, with stricture so as to cause marked periodic urinary obstruction. Such a stone shadow will frequently be either misinterpreted or entirely overlooked in the roentgenogram.

4. Least in frequency among the causes of roentgenographic failure should be considered the character of the stone. Whether or not a stone is demonstrated depends largely on the calcium content. Although a stone composed of uric acid or phosphatic elements may not cast a distinct shadow, nevertheless the great majority of stones are composed of a mixture of calcium with the various other salts and the absence of a shadow is usually to be explained by the previously mentioned reasons.

Localization of Stones.—A review of the 230 cases with operation for stone in the ureter demonstrates the occurrence and position of the stone as follows:

Ureteropelvic juncture	26 cases
Upper third	25 cases
Middle third	1 case
Lower third	159 cases

The last group was subdivided as follows:

Iliac crossing	4 cases
Pelvic portion	90 cases
Ureterovesical juncture	41 cases
Intramural	22 cases
Meatus	2 cases
Not definitely located	3 cases

It will be seen that 159 (74 per cent.) of the 214 cases localized were found in the lower third of the ureter and that the greatest number were found in the so-called pelvic portion of the ureter, which term includes that portion of the ureter extending from the point of narrowing at the iliac crossing to the ureterovesical juncture. The majority of the stones in the pelvic portion were not lodged exactly at the point of narrowing at the ureterovesical juncture, but a short distance above it. The same is true of the stones described at the ureteropelvic juncture, the majority of which were found a short distance above the point of narrowing. The stone was impacted within the wall of the bladder itself in 20 cases, a proportion of operative cases which will no doubt be reduced in the future as the result of the recent improvement in operative cystoscopy. The small number noted which were lodged at the meatus was due to the fact that although a number of others were so situated, they were all removed by means of endoscopic technic. The small number found at the point of iliac crossing and in the middle third is surprising. It is difficult to explain the large number of stones found in the upper third of the ureter. They were found well below the point of narrowing and at the ureteropelvic juncture, and their presence on exploration offered no explanation for this unusual condition. The majority of such stones, however, were of considerable size. The average size found in the lower third of the ureter was much smaller than those found in the upper ureter. As a general rule, stones situated in the ureter at points other than those of natural narrowing were larger and caused more renal destruction than the others. This series does not include a number of stones which were demonstrated at the preliminary roentgenographic examination to be situated in the ureter, but which at operation or subsequent to ureteral

catheterization were displaced into the pelvis of the kidney when they were removed.

Occurrence of Stone.—In regard to the occurrence of stone: in 134 cases it was found in the left ureter and in 144 cases in the right—practically no difference as to the side. Single stones were found in 261 and multiple stones in 17 cases (93 per cent.). Stone occurred in both ureters in 6 cases; in the kidney on one side and in the ureter on the other in 11 cases; or a total bilateral occurrence of 17 (6 per cent.). It is evident that bilateral occurrence of stone in the ureter which comes to operation is much less than that in the kidney. This discrepancy may be at least partially explained by the frequent spontaneous passage of ureteral stones. Stone occurred in the kidney as well as the ureter on the same side in 12 cases (4 per cent.).

It will be noted that the stone in the ureter was not found on exploration in 13 cases. In 3 of these cases the stone was pushed into the bladder during operation and passed afterward. In 3 other cases the stone was found to have been passed during the few days intervening between the clinical examination and the time of operation. In 4 cases the stone was passed after the operation. In 3 cases no stone was found at operation and there was no subsequent history of a stone having been passed, which can be explained only by error in the diagnosis. It is obvious, therefore, that should there be an interval between the last clinical examination and the operation, another secondary roentgenoscopy should be made just prior to the operation, since the stone may either have passed during this interval or it may have greatly changed its position. Particularly is this true if a cystoscopic examination with ureteral catheterization has been made. The patient should be questioned whether or not severe pain has been experienced following examination. It should also be remembered that in spite of the absence of colic, the position of the stone may have greatly altered.

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CLINICAL REVIEW OF 240 CASES OF NON-SURGICAL INFECTION OF THE KIDNEYS AND URETERS *

GILBERT J. THOMAS

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In an attempt to discover the predisposing factors, if any, in non-surgical infection of the kidneys and ureters, and to determine the relative value of the present modes of treatment, antecedent infections, previous operations, etc., have been considered in this study. The symptoms of onset and those of most common occurrence during the progress of the disease have been analyzed together with cystoscopic and bacteriologic findings. Stones in the bladder, kidney, or ureter and obstruction in the lower urinary tract have been excluded.

Such infections, except those due to obstruction in the lower urinary tract, are hematogenous in origin. In the infections due to obstruction the lymphatics probably play a part in carrying the infection to the kidney. It is possible that they, also, are of hematogenous origin, and that obstruction lessens resistance by mechanical means and is the predisposing factor, not the cause, of the infection.

Brewer¹ states that all renal infections are hematogenous, including those that come from an infection primary to the bladder. Sweet and Stewart,² after careful anatomic and experimental study, have concluded that the lymphatics of the bladder, ureter, and kidneys anastomose rather freely, and that they can carry infection from the bladder to the kidney. They believe this route of infection is frequently the one by which the pelvis and parenchyma

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of the kidney become infected from the infection in the bladder. Cabot³ and others believe that cases in which there are a great many elements in the urine and few symptoms are lymphatic in origin, while those showing few such elements and marked general symptoms are hematogenous in origin.

The present study comprises a review of 240 patients who received urologic treatment in the Mayo Clinic from January 19, 1910, to January 19, 1915; 32.8 per cent. were women and 67.2 per cent. men. The average age of onset was 30.3 years. The duration of symptoms ranged from two weeks to twenty years. Twenty-six per cent. of the patients did not give a history of previous diseases; 18 per cent. had infections of the genital tract, giving a history of gonorrhea or pelvic infection; 12 per cent. had had a previous attack of typhoid fever; 9 per cent. gave a history of childhood infections; 6 per cent. of pneumonia; 3 per cent. of tonsillar infection; 4 per cent. of arthritis and rheumatism; 4 per cent. of scarlet fever; 2 per cent. of empyema of the antrum and chronic abscesses; 2 + per cent. of syphilis, and 5 gave a history of severe abdominal injury. The remaining patients gave histories of infections as follows: Lung, 1; ruptured urethra, 1; phimosis, 1; dysentery, 1; malaria, 4; pregnancy, 2, etc.

Of the 240 cases, the first symptom complained of was frequency of urination; it was also the most common symptom, being present in 76 per cent. of cases, and varied in intensity from voiding every ten minutes to one or two times per night. In 37 per cent. pain was the primary symptom. In the analysis of pain as a symptom it was found that severe lumbar attacks were complained of in about 20 per cent. of all the cases; a dull ache across the lumbar area and sacrum was frequently described. Epigastric, lower abdominal, and vesical pain was frequent. Painful and burning urination occurred at some time during the history in 60 per cent.

Hematuria was the first symptom in 7 per cent., and it was noted at some period of the history in 41 per cent. of the cases. In 2 per cent. temperature and chills were the first symptoms, these symptoms being present in 25 per cent. of cases.

Pyuria was a primary symptom in 2 per cent. An appreciable loss of weight was noted in 41 per cent. Gastric and duodenal lesions were suspected in a number of cases because of reflex pain, which was probably of renal and ureteral origin. In a small percentage these attacks were persistent, unrelieved by urologic treatment, and required surgical measures.

Cystoscopic Diagnosis.—Cystoscopic examination demonstrated the existence of bilateral infection in 174 (73 per cent.) patients. The infection was confined to the right side in 6 per cent.; in 18 (7 per cent.) the infection was on the left side only. Fifty-one cases were diagnosed as pyelitis, 5 of which were of a chronic, bleeding type. In our experience the differential diagnosis between pyelitis and pyelonephritis has been rather difficult. Acute repeated attacks, with microscopic findings in the urine, that quickly subside with or without treatment, may be regarded as infections of the pelvis alone. The chronic refractive type, which shows few elements in the urine, may be considered as pyelonephritis. The infection found in pregnant women is usually a pyelitis; it is to be noted that these patients are relieved as soon as the uterus is emptied and good drainage restored. In only a few of these cases does the parenchyma become involved. An illustration of the somewhat acute temporary infection of the pelvis, or pyelitis, is shown in the many instances of post-nuptial infection. These cases quickly clear up by means of urotropin and other simple methods because the parenchyma is probably not involved. We have observed two very interesting cases of post-operative infection of hematogenous origin in which the *Bacillus tuberculosis* was found to be the causative organism. Both patients developed acute cystitis and showed bacilli in specimens of urine from the bladder. In one there were tubercle bacilli in both ureteral specimens. These patients were relieved by urinary antiseptics and hygienic treatment. Repeated examinations after the acute symptoms had subsided failed to demonstrate the organisms. One patient has remained well for one year and no focus of infection can be found. There had been a tonsillectomy a short time preceding the onset of cystitis. One patient was well one month

after the acute onset. Guinea-pig inoculation was negative in one after three months.

In our hands renal functional tests have not always proved satisfactory in the differentiation between pyelitis and pyelonephritis. Equal function in the two kidneys has frequently been observed in cases in which the pyelograms demonstrated one kidney badly damaged. In those showing infection active on one side and inactive on the other, the difference in function may not be great enough to be of value. In some cases one kidney with a quantity of pus would show as large an output of the drug as the kidney with no bacteriologic or chemical findings. However, when one kidney is largely destroyed, the difference in function when using the dyes has been great enough to direct suspicion to the destroyed kidney.

Pyelogram.—The pyelogram will differentiate a marked infection of the parenchyma from one in the pelvis. Infection in the parenchyma shows but slight inflammatory changes in the pelvic outline, while a pelvic infection usually shows marked inflammatory changes. This means of differentiation has also been of considerable aid in separating the cases of actual pyonephrosis from the milder grades of infection, 7 cases having been found in which one kidney was largely destroyed. It may also be of value in determining the etiologic factor. Congenital anomaly in the urinary tract, which may have been an etiologic factor, was found in four cases. Obstruction in the lower ureter was demonstrated by means of the pyelogram in several cases as the probable cause of renal infection.

Cystitis.—A marked degree of cystitis was noted in 16 per cent. of the cases, while, as mentioned above, the most common symptom (frequency of urination) was noted in 76 per cent. of cases. The bladder does not always show marked signs of infection, as is shown by this series, wherein 25 per cent. had no cystoscopic evidence of cystitis. All of these patients, however, had varying amounts of pus in the urine, yet 34 per cent. had no symptoms referable to the bladder. A considerable number of cases of renal infection have been diagnosed only after careful and repeated

cystoscopic examinations. Many showing only a few pus-cells at the time of the first examination, on reëxamination showed larger amounts of pus from one or both kidneys and vice versa. A number of patients with irritability of the bladder and no microscopic findings in the urine have shown bacterial growth from catheterized urine from both kidneys. In our experience cystitis is not a necessary finding in renal infection. Vesical irritability is a more constant sign than cystoscopic evidence of cystitis, but both these findings may be absent in the presence of a renal infection.

Bacteriologic Examination.—Records of complete bacteriologic examinations were available in 95 cases; 63 per cent. were of the colon group. The other organisms were pyocyaneus, Micrococcus urea, pneumococcus, streptococcus, and the staphylococcus group. It is probable that the *Bacillus coli* is a secondary invader in a large percentage of these infections. The offending organism and its toxins probably lessen the resistance of the kidney so that the colon bacillus, which is constantly passing through the kidney, becomes pathogenic. Many writers are of the opinion, however, that the pyelitis of pregnancy and the infections which accompany constipation are primarily of colonic origin. The stagnation due to pressure from the uterus on the intestine and resulting constipation are factors which probably predispose the kidney and ureter to colon infection. The pressure of the uterus on the ureters interferes with their function, and this lessens their resistance to infection.

When symptoms are suggestive of tuberculosis, guinea-pig inoculation is desirable. This was found necessary to complete the diagnosis in 48 cases. In our experience absence of pus or no growth on culture does not necessarily mean a single infection. Inactive infection has frequently been found on one side by microscopic and bacteriologic examinations, which could be demonstrated at other times as being active. It would be well to consider a non-tuberculous, non-calculous, unilateral infection as part of a bilateral condition until, by pyelographic and cultural examinations, one kidney has been proved to be sound.

In making cultures of urinary infections contamination of the specimen obtained would frequently negate the value of the bacteriologic examination. Such contamination, in our experience, has been due to faulty technic in that all instruments used were not completely sterilized. Ureteral catheters are not easily sterilized, as may be proved by cultures made from bits of catheters which are in daily use and which are thought to be sterile. The ureteral catheter should be boiled or should be made sterile in some manner, so that when sections are introduced into several culture-media no growth can be obtained. The use of unsterile lubricants is also a frequent source of contamination. Catheters or containers which have just been removed from an antiseptic solution have been the frequent cause of a report of no growth when later examinations demonstrated organisms present. A small amount of such solutions in culture-media will prevent growth. Cultures should be grown both aërobically and anaërobically.

Treatment.—A careful search for foci of infection, such as tonsils, teeth, abscesses, furunculoses, bone infections, etc., should be made before any local or urologic treatment is instituted. Chronic abdominal complaints and any pathologic condition which might harbor infection should be searched out and completely eradicated. As mentioned above, 26 per cent. of patients gave a history of having had no serious illness or infection which might pave the way for chronic renal disease. It is safe to assume that many of these patients had forgotten the furunculosis, the severe attack of tonsillitis, the chronic suppurative ear, the chronic infectious diseases of childhood which at the time seemed trivial. It is also probable that organisms frequenting tonsils, carious teeth, appendix, or gall-bladder may be so changed in character, as Rosenow⁴ has demonstrated, as to have a special affinity for the urinary organs at certain times. The ever-present colon bacillus quickly outgrows the organism of primary infection, so that in most chronic cases the true offending bacteria are not always found. Auto-genous vaccines were given when obtained in pure culture, and when the tolerance of the patient would permit.

Local treatment consists of regular lavage, at four- or five-day intervals, of the kidney pelvis, ureter, and bladder. For this purpose silver nitrate, argyrol, colloidal silver, protargol, and silver iodid have been used. Many of the patients were given urinary antiseptics by mouth. Silver nitrate, beginning with 0.5 to 1 per cent. in strength and increasing to 2 or 3 per cent., has proved the best solution for lavage of the pelvis. Aluminum acetate, in our hands, did not prove efficacious, and was unsatisfactory because of the reaction it frequently occasioned even when freshly made and diluted. Weak solutions of argyrol and the other colloidal silver solutions were used in the severe acute infections where reaction was feared.

Surgery becomes the logical treatment when a single infection is persistent with marked constitutional symptoms, even in the presence of mild infection on the other side. Inflammatory obstruction of the ureter, pyelitis granulosa with persistent bleeding, and extensive distention from infection, with destruction of renal tissue, are also indications for surgical interference.

To ascertain the effect and permanency of the different methods of treatment a circular letter was sent to each of our patients and 150 definite answers were received. A tabulation of these answers shows that the condition was stationary in 44 (29 per cent.) of the patients; improved in 70 (46 per cent.); and that recovery was complete in 28 (18 per cent.). Eight of these patients have since died, and the reports show that in over 50 per cent. the fatal outcome was probably due to severe renal lesions.

A more minute analysis of these answers relative to the combinations of treatment employed showed some interesting facts. Of the 26 patients in whom vaccines alone were used, 6 have apparently recovered, 11 have improved, and 5 showed no improvement. In 8 patients in whom lavage of the pelvis alone was used by any of the above-mentioned solutions 2 recovered, 2 improved, and 4 remained stationary.* Urinary antiseptics used alone in 31 cases caused 4 apparent recoveries, 13 improvements, and 19 cases

* Silver nitrate was used in over 90 per cent. of cases where lavage was practised.

unimproved. With the combination of vaccine and pelvic lavage, only 2 patients recovered, 20 improved, and 9 did not improve. Thirty-one patients in all were so treated. Vaccines and urinary antiseptics in 19 patients showed 6 recoveries, 8 improvements, and 5 unimproved. Eight patients in whom vaccine, lavage, and urinary antiseptics all were used showed 2 recoveries, 4 improvements, and 2 non-improved. Eight patients received no treatment, three of whom apparently recovered, two improved and three remained stationary. Seven patients were operated on, four showed surgical lesions in the urinary tract; two recovered completely, and five improved. The tabulated results of treatment are as follows:

METHOD OF TREATMENT	Re- COVER- ED	Im- PROVED	STA- TIONARY	DIED
Autogenous vaccine only.....	6	11	5	..
Pelvic lavage only.....	2	2	4	..
Urinary antiseptics only.....	4	13	19	..
Vaccines and lavage.....	2	20	9	..
Vaccine and urinary antiseptics.....	6	8	5	..
Lavage and urinary antiseptics.....	0	1	1	..
Vaccine, lavage, and urinary antiseptics.....	2	4	2	..
Bladder lavage only.....	1
No treatment.....	3	2	3	..
Surgery.....	2	4	1	..
Death from renal insufficiency.....	4
Death from other causes.....	4

It will be noted in the above tabulation that the greatest percentage of recoveries is found in the "vaccine only" column. The patients who had this treatment and had no lavage of the pelves had very mild infections. Many of them showed a small amount of pus in the urine, and cultures were obtained only after repeated trials. These patients would probably have recovered without treatment.

The rather large group of patients who received antiseptics only were advised to have either pelvic lavage or vaccine, but as this treatment is somewhat troublesome and could not be obtained at their homes, they continued the medicine by mouth only.

Where lavage was used, the number of complete recoveries is small. These cases have not been considered free from infection until the urine was free from microscopic pus, and until repeated cultures were negative. As most of our cases were irrigated with silver nitrate, pus could be obtained at any time, but cultures were repeatedly negative after the treatment had progressed for varying lengths of time. It is probable that the silver nitrate was the cause of microscopic pus in many cases in this group, and that, as many of them were culturally free from organism, they should be considered temporarily cured.

CONCLUSIONS

1. Infections elsewhere in the body are predisposing factors in infections of the kidneys and ureters.

2. Seventy-three per cent. of these infections are bilateral at the onset of the disease. The lack of pus or bacterial growth of the catheterized urine does not always mean non-infection, but non-active infection.

3. Pyelography and guinea-pig inoculation may be necessary to identify tuberculous infection and to differentiate the unilateral from the bilateral infection. The renal functional tests were frequently not of much value in differentiation between the locations of the infection.

4. Very careful technic should be followed in obtaining specimens for culture, as contaminations frequently occur and negate the bacteriologic findings.

5. Treatment affords relief or cure in 64 per cent. of cases, and should always be carried out in some form. No single method will give results in every case, so that all methods should be tried. Pelvic lavage has probably been the most satisfactory, but whenever possible, should be used in conjunction with an autogenous vaccine. Nephrectomy, when necessary, affords complete recovery from general symptoms, and improvement or cure of the infection in the remaining kidney.

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ANURIA FOR FIVE AND ONE-HALF DAYS IN A PATIENT ON WHOM LEFT NEPHRECTOMY HAD BEEN DONE *

GILBERT J. THOMAS

CASE 58,357.—Man, aged forty-three years. Examined July 3, 1915. Occupation, locomotive engineer.

Nephrectomy of the left kidney for pyonephrosis was done at the Mayo Clinic September 16, 1911, at which time the patient was carefully examined, and the right kidney found to be normal. Three months after the operation he returned home and to his work. He had gained in weight, and seemed to be in good health.

Two years after the operation he had an attack of acute right renal pain and anuria lasting for five hours. This cleared up without treatment, and he had no further trouble until two weeks before coming to the Clinic the second time (July 3, 1915), when he began to feel bad. He lost his appetite, had a coated, dry tongue, was constipated, and stated that he felt "queer" all over. His home physician thought he was suffering from malaria, and prescribed accordingly. Six days after the onset it was noted that no urine had been passed for five and one-half days. His bladder was catheterized several times without result. Hot packs, saline, and forced water were used during the next thirty-six hours, and he voided 62 ounces of urine. Suppression was complete for another twenty-four hours, and during the railway journey to Rochester (500 miles) the patient voided but one ounce of urine. At no time during the two years had there been any pain that might have been due to obstruction of the right ureter.

At the second examination he was very weak, and was carried on a stretcher. The skin was muddy in color and very dry. Mouth, dry; tongue, coated, dry, and furred; breath, foul and somewhat urinous; teeth, in bad condition. Dulness in right chest, posteriorly and anteriorly, with no breath-sounds, and no

* Reprinted from the *Journal-Lancet*, 1915, xxxv, 667-68.

fremitus over these areas. Left chest normal. The heart-sounds were good, and no enlargement could be demonstrated. Pulse-rate somewhat increased. The abdomen was prominent, and there was general tenderness. These findings were more marked on the right side, where there was also a distinct sense of resistance. The abdominal organs could not be palpated. The genitalia were normal. Acute, inflamed, protruding piles made a rectal examination impossible. No edema of any part of the body.

The patient's condition made immediate relief necessary, and he was prepared for cystoscopy. Since this patient had been free from pain and the history of the onset was somewhat gradual, nephritis was at first thought of, but relief by ureteral catheterization was the logical measure to be tried first, and decapsulation and exploration of the upper ureter to be attempted if this failed. The bladder was normal; the right ureteral orifice was easily found, but no urine was seen during an observation of fifteen minutes. A No. 6 flute-end catheter was introduced into the ureter, and met resistance at its upper third. By a gradual and careful manipulation the resistance was passed, but for about two or three minutes no urine could be obtained through the catheter. Gentle pressure over the kidney was then applied, and a syringe used for suction at the end of the catheter, which resulted in the passage of about two drams of a thick, ropy mucus, followed by a continuous stream of slightly hemorrhagic urine. Not knowing the cause of obstruction and fearing recurrence, the cystoscope was removed, leaving the ureteral catheter in place. During the first twenty-four hours the patient passed quantities of clear urine, and his abdominal prominence and rigidity were at once relieved. He felt better within fifteen minutes after the ureteral catheter began to drain. By frequent irrigation with warm boric-acid solution the catheter was kept open for three days. During the last twelve hours of this time the patient seemed to void urine normally, and, since the catheter had slipped considerably, it was removed.

The patient was advised to remain in bed and on his back for two or three days. There was no recurrence of the anuria, and he was then allowed to get up and about. Although somewhat weak, he felt well, and his general condition was greatly improved. Fourteen days later he was apparently normal, and wanted to go to work. At this time Roentgen and cystoscopic examinations showed the kidney and ureter free from shadows and the kidney functioning normally. The functional test gave 51 per cent. of phenolsulphonaphthalein secreted in two hours. We were much

surprised not to find evidence of residual urine in the pelvis at this time. The patient was allowed to go home, but advised not to work for at least one month.

The points of interest in this case are the following:

1. Complete anuria for five and one-half days, and the total amount of urine secreted in nine days, 64 ounces.
2. The patient had but one kidney, the other having been removed some time before for pyonephrosis.
3. No history of pain during the present attack.
4. The cause of obstruction not known. No stones or fragments were passed before or after cystoscopy. Roentgen ray was negative.
5. Relieved by permanent ureteral catheter.
6. The patient in apparently normal health after ten days, and no damage to the kidney demonstrated.

PROCEDURES FOLLOWING NEPHRECTOMY*

WILLIAM J. MAYO

I. THE TRANSPERITONEAL CLOSURE OF DUODENAL FISTULAS FOLLOWING NEPHRECTOMY

Injuries to the third portion of the duodenum may occur during right nephrectomy. In a previous communication I¹ reported three such cases. The injury is most apt to occur in the attempt to secure the pedicle for the purpose of ligation, and is especially liable to happen when the pedicle is greatly infiltrated with inflammatory products and fixed in close relationship with the duodenum. Under such circumstances the vascular pedicle of the kidney may slip from the retaining forceps or ligature during attempts at ligation. Efforts to grasp with tooth forceps the bleeding vessels in the bottom of the wound may result in the duodenal injury. The perforation follows after some days, due to necrosis of the devitalized portion of the duodenum.

All the patients reported on in my first communication died within three weeks from the date of the injury as the result of rapid failure of nutrition. At that time I advised that no attempt be made to close the fistula from behind and that no time be wasted with the expectation of spontaneous closure of the fistula. Instead, as soon as the diagnosis should be established, the abdominal cavity should be opened through the anterior abdominal wall, the peritoneum incised to the right of the curve in the duodenum, the duodenum itself elevated from its retroperitoneal bed at its outer side, and the duodenal opening closed directly by suture. Of the three cases reported, in two the duodenal injury occurred at the primary operation and in one it was secondary. In this latter

* Reprinted from Jour. Amer. Med. Assoc., 1915, lxiv, 953-957.

case the physician in charge of the after-care of the patient used a sound to explore a sinus which formed following the nephrectomy, and, since the duodenal fistula appeared immediately after the

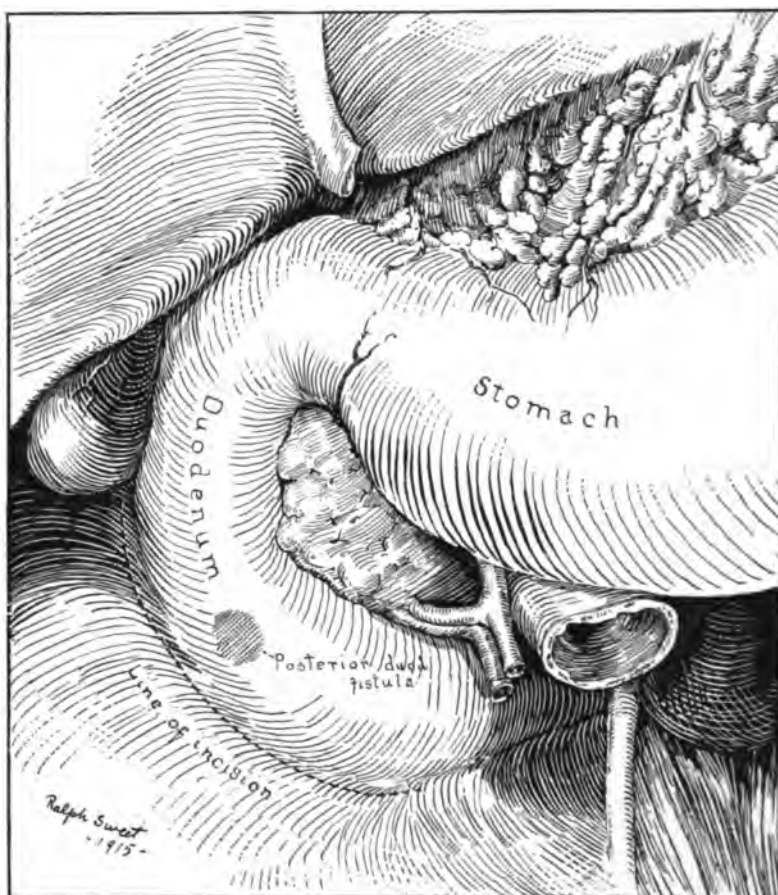


Fig. 106.—Site of duodenal fistula on posterior wall of duodenum, showing line of incision through peritoneum.

sounding, it was thought that during the manipulation the sound was plunged directly into the duodenum. The case herewith reported belongs to the latter type of injury.

CASE 108,397.—H. C. H., a man aged forty-six, was admitted to the Clinic June 17, 1914. Roentgen examination revealed a single stone in the left kidney and multiple stones in the right kidney. Cystoscopic and ureteral examination showed slightly infected urine and moderately diminished function in the left kidney, while a pyonephrosis with destruction of function was evident in the right kidney. It seemed advisable first to remove the stone from the left kidney, thus restoring it to good function, and to remove the right kidney at a second operation. On June 30, 1914, a stone was removed from the left renal pelvis. The patient made an excellent recovery from this operation and on August 26, 1914, the right kidney was removed.

Both operations were done through posterior lateral incisions. The wound in the left side healed primarily and was sound before the right nephrectomy was undertaken. On the right side there was primary union; but during the fourth week, without premonitory symptoms, a sinus formed in the wound and continued until the date of reëxamination on January 4, 1915. The history showed that when the sinus first formed it caused comparatively little inconvenience, but later the patient developed symptoms of septic infection, although without any increase of the local signs. There was an evening temperature of from 101° to 103° F., with occasional chills, general malaise, and loss of flesh. This continued for some weeks, then the patient gradually improved and was able to be about, but the sinus continued to drain a peculiar purulent substance which had somewhat the appearance of gelatin. The total amount discharging from the sinus in twenty-four hours did not exceed one or two drams.

On January 6, 1915, under ether anesthesia, I enlarged the sinus sufficiently to introduce a finger into the cavity, which was of considerable size and quite unlike the ordinary drainage cavity due to sepsis. The space was rather soft and indefinite and there was no apparent retention of secretion in the cavity. A strip of iodoform gauze was placed through the opening. No instrument of any kind was introduced into the cavity. On January 7th there was a very considerable discharge of light yellowish fluid. January 8th the piece of gauze was removed and there was an abundant discharge of bile, pancreatic and duodenal secretion, and some particles of food. It was evident that there was a duodenal fistula in the retroperitoneal portion of the duodenum (Fig. 106), but how produced was a mystery.

The patient was at once taken to the operating room, the

abdomen opened by an incision through the middle of the upper right rectus muscle, the hepatic flexure and transverse colon



Fig. 107.—Showing fistula opening dissected from posterior attachment and brought into view.

drawn down, the liver and gall-bladder up, and an incision made through the peritoneum to the outer side of the duodenum, beginning at the level of the papilla of the common duct and extending

around well to the spine. The duodenum was carefully dissected from its posterior attachments until the fistula, which was of sufficient size to admit the end of the finger, was completely separated

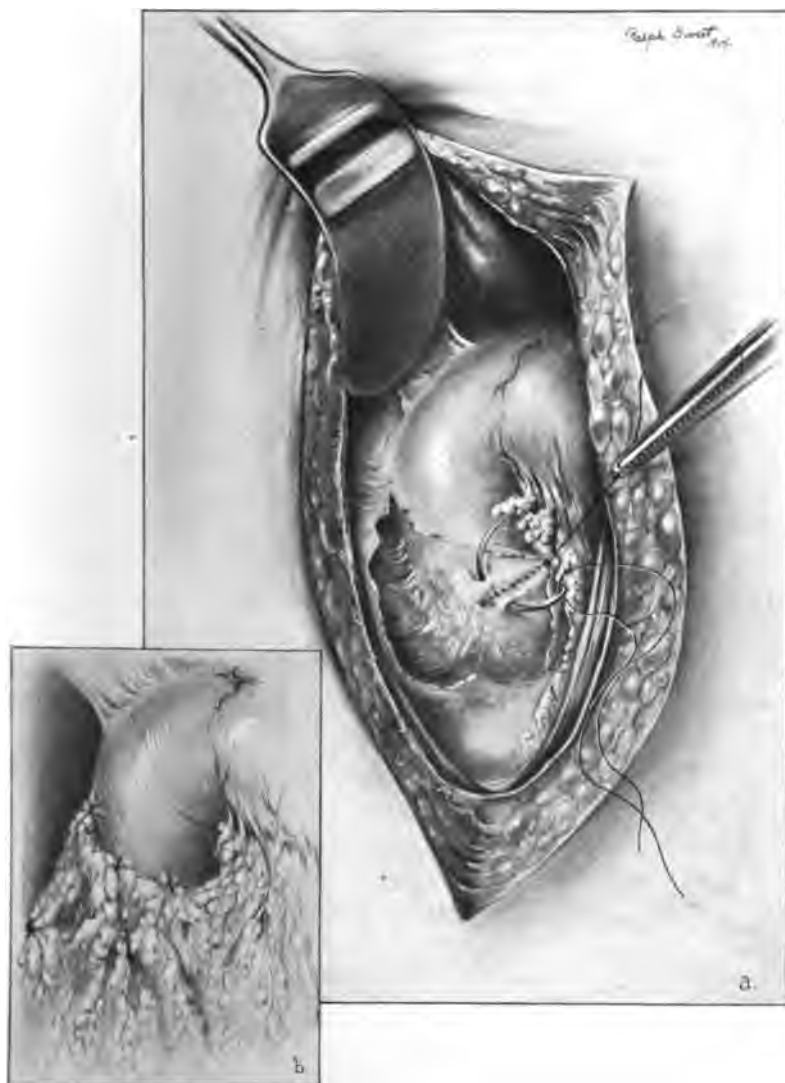


Fig. 108.—a, Suturing of fistula; b, protecting sutured area with omental graft.
'15—23

and exposed in the wound (Figs. 107 and 108). The fistula was sutured transversely with chromic catgut and interrupted fine silk. The omentum was drawn over the sutured duodenum and the tip was passed into the posterior opening, from which the fistula had been separated, and attached in position with a few catgut sutures. A rubber-tissue drain was introduced through the sinus opening into the posterior cavity. The entire operation occupied but a few minutes and was remarkably easy of accomplishment. The patient made an uninterrupted recovery.

This case brings up the very interesting question: What was the cause of the fistula? The original nephrectomy was subcapsular, and certainly no direct injury to the duodenum occurred during the operation, or the fistula would have developed at once. The fistulous opening on the inner posterior aspect of the duodenum extended well up into the edge of the pancreas, as shown by the operation for its closure. It is probable that chronic infection existed in the pedicle at the time of the nephrectomy, and this infected area led to localized necrosis in the margin of the head of the pancreas, and the curious nature of the cavity and its discharge was the result of a little pancreatic secretion in connection with the necrosis. The injury at the time of the exploration certainly could not have been inflicted directly on the duodenum, since, at the time of the closure of the fistula, with the right hand in the abdomen, the first finger introduced through the posterior wall of the abdomen into the cavity and the left forefinger introduced through the lumbar sinus could not be made to meet. It is evident, therefore, that this condition existed as the result of some slow infection, and, in the manipulation, separation of a necrotic area in the duodenum was indirectly brought about.

The transperitoneal approach to the fixed portion of the duodenum has been advised, although in my somewhat superficial examination of the literature I did not find any reported cases of duodenal injury during right nephrectomy. Nevertheless, I am sure that these injuries have occurred, but the seat of the fistula's opening has not been recognized as being duodenal.

Summers² treated a gunshot injury in the retroperitoneal part

of the duodenum by the transperitoneal route and gave an excellent summary of the somewhat scanty literature which existed at that time.

Kanavel,³ in a careful study of the method of approach to this portion of the duodenum, a method which he used for traumatic rupture, brings the literature up to date. He advised that attack be made from below the colon through the inferior layer of the transverse mesocolon, and this undoubtedly is wise when that portion of the duodenum is injured which lies over the spine toward the duodenojejunal angle. For this particular injury, however, the method of approach from above the transverse colon is so easy and satisfactory that I think it will be the method of choice in such cases. Considerable movability is possessed by this part of the duodenum, its blood supply and fixed portion lying against the pancreas on the inner side to the left, so that almost its whole circumference can be brought into view through this incision.

II. THE TWO-FORCEPS METHOD FOR THE LIGATION OF VASCULAR PEDICLES, WITH SPECIAL REFERENCE TO NEPHRECTOMY

In the sixteenth century, Ambrose Paré, the Huguenot physician of Catharine de Medici, first applied the ligature to check hemorrhage, and the ligature still remains the method of choice as a means of controlling hemorrhage. One might suppose that experience for nearly four hundred years with this effective device would have resulted in a technic nearly perfect, but this is far from the truth. To-day, the most common avoidable cause of death following surgical operations is the effect of hemorrhage, although deaths on the operating table directly from this cause are rare. The common cause of so-called surgical shock is collapse from loss of blood, and traumatism of important structures in hasty attempts to control hemorrhage. Secondary shock usually means a bleeding vessel overlooked at the time of operation, vessels improperly ligated which commence to bleed after the patient has been placed in bed and the normal vascular tonus has been restored,

or massive sepsis from a viscus injured in controlling hemorrhage. Any hospital that is not securing a high percentage of necropsies following surgical fatalities will have a number of unexplained deaths in which, directly or indirectly, hemorrhage is the cause, although not suspected. The surgeon whose work is not checked by necropsies in deaths following his operations usually has many ingenious explanations as to the cause of death, explanations which may appear reasonable and scientific and which occasionally may be correct.

At present, in our clinic, necropsies are secured in more than 90 per cent. of all deaths. Either the operating surgeon or the first assistant is present at the necropsy. Thus we secure an enormous amount of information, much of it humiliating to the surgeon and much of it concerning failure of hemostasis.

People die from very real things. When I hear of some surgical fatality explained in some abstruse theoretic manner, I suspect that a postmortem was not made or, if made, that it was done by a pathologist not competent to judge of the conditions present. For this reason I should urge that the postmortem be held by a competent pathologist who is interested in getting at the facts rather than in endeavoring to conjure up excuses for the surgeon, and that by all means the operating surgeon or his first assistant shall take part in the postmortem or at least be present. The surgeon should discuss necropsy findings in his clinic, so that by example and precept other lives may be saved. In no other way can he so well atone for his shortcomings. As Lincoln said in his Gettysburg address: "These dead shall not have died in vain."

Internal hemorrhage, especially in the abdomen, is not always classic in its symptoms. The blanching, restlessness, air-hunger, subnormal respiration, and increasing rapidity of pulse may not be prominent features. If the hemorrhage is somewhat slow, the patient may not die for several days. Again, the hemorrhage may not be of itself lethal, but may be responsible for a later sepsis by furnishing a culture-medium for a few germs which may have been present and which the tissues otherwise might have been capable of destroying. For this reason any improvement in the technic

of hemostasis, however small, has a value even though it only keeps our attention constantly directed toward the necessity for reliable hemostasis.

In the attempt to tie a deeply placed pedicle it occasionally slips out of the grasp of the ligature, permitting rapid and exhausting hemorrhage. This is especially true of the pedicle of the kidney. The surgeon reaches in with forceps and with considerable difficulty, in a pool of blood, succeeds in grasping the vessels. Forceps used in this way are dangerous. In these hurried attempts, if the operation be a right nephrectomy, the vena cava or the retroperitoneal portion of the duodenum may be injured. Vessels the size of the renals can be easily caught and held with the fingers. The spurting of blood leads the fingers directly to the vessels, and forceps can then be applied with care and circumspection.

If the two-clamp method be used for the purpose of ligation, slipping of the pedicle should not occur. The kidney is first exposed through an appropriate incision, such as the posterolateral, which I have previously described.⁴ The perirenal fat is separated, the ureter divided between ligatures, and the ends sterilized. Forceps should not be left on the portion of the ureter which is to be removed with the kidney, as they may slip or tear off and the wound be soiled from the contents of the renal pelvis. The fragment of ureter to be removed should be dissected well up to the pelvis of the kidney, that it may not be tied into the vascular pedicle. The vascular pedicle is now exposed by careful removal of its surrounding fat (Fig. 109). In many cases the vessels can be ligated separately, but if the pedicle is thick and deeply placed, or if the operation be a subcapsular nephrectomy, two forceps are placed on the proximal side, if possible about $\frac{3}{4}$ inch apart, and the kidney cut away. A ligature is then thrown around the pedicle beneath the deeper pair of forceps. This pair of forceps is removed so that the ligature slides into the groove made by the forceps and is tied, while the pedicle itself is still safely retained in the distal forceps (Fig. 110). A second ligature can then be placed and the distal forceps removed as the knot is pulled tight. Mass ligation of this type, theoretically, is not as good as ligation of the separate

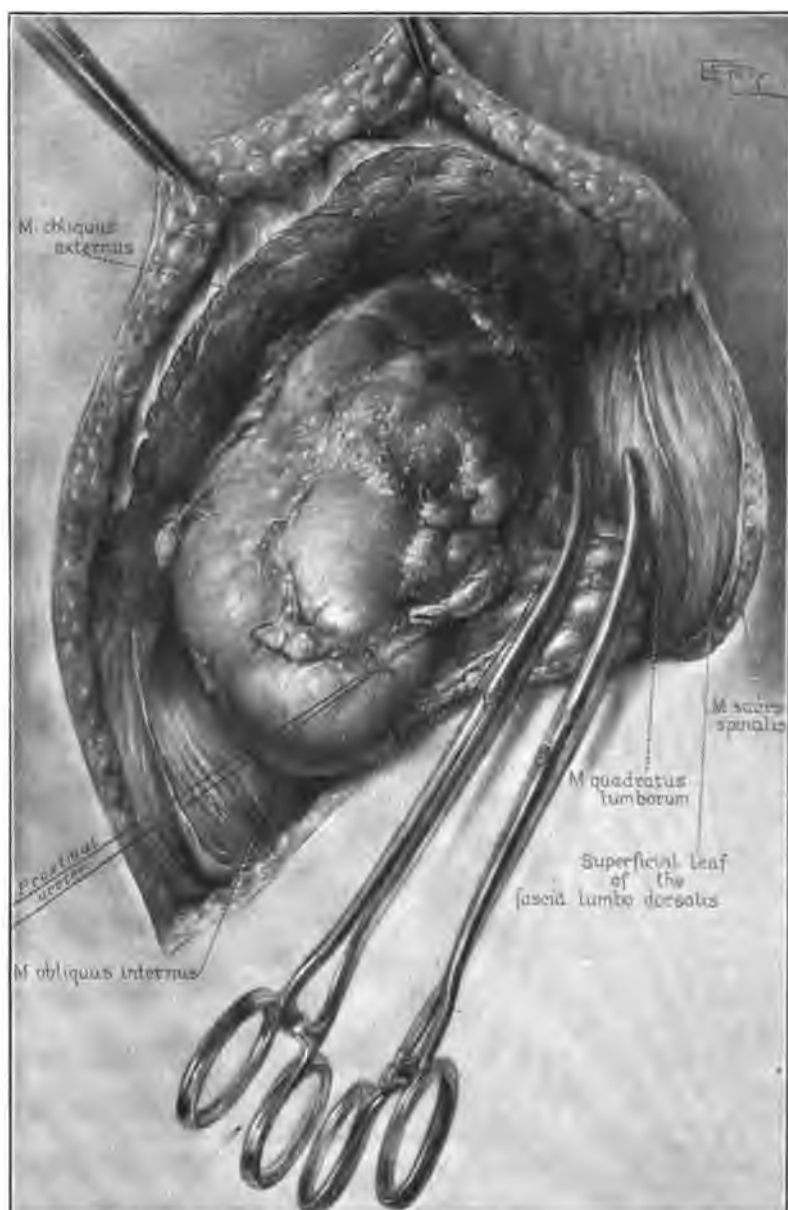


Fig. 109.—Kidney drawn up with two clamps in position; ureter dissected well up to pelvis and hilum of kidney.

vessels; but if sepsis or tuberculosis is present, direct ligation of each vessel cannot be accomplished so safely. If done blindly, the renal veins may be penetrated and thus, if the wound has been soiled, sepsis or tuberculous infection may be carried directly into the vein. In our early experience there was one death from general septicemia and one from acute miliary tuberculosis for which I believe direct venous infection from the needle carrying the ligature was responsible.

The two-forceps method is especially applicable in nephrectomy and splenectomy. In the latter operation, care should be taken that the tail of the pancreas does not extend up into the hilum of the spleen; if so, it must be dissected out before the clamps are placed in position.

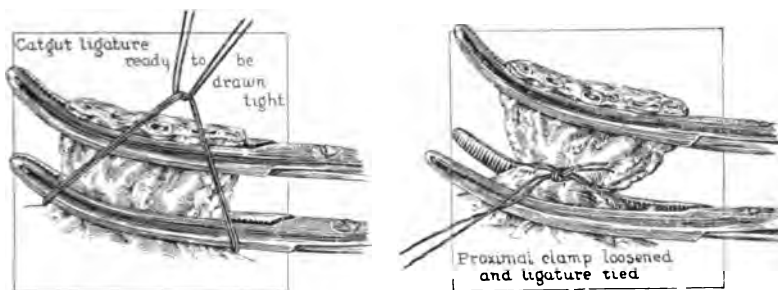


Fig. 110.—Method of procedure in two-forceps ligation of pedicle.

Thus far I have succeeded in using the two-forceps method on the renal pedicle. In some other situations only a single pair of forceps can be applied to a pedicle and not always satisfactorily at that, as the point of the forceps may not project far enough beyond the tissues within their bite to secure a firm hold for the ligature; or the pedicle may lie very deep so that the ligature cannot be passed beyond the point of the forceps. In such a case it is necessary to use a ligature on a needle. The needle, threaded, is passed through about one-fourth of the diameter of the pedicle. Then, with a single knot, the tissues are brought sufficiently tight under the end of the forceps to secure a good hold. The ligature is then brought around the opposite side of the pedicle and a single

knot made. The forceps are slowly loosened and the ligature pulled home; both sides of the pedicle are thus drawn tight and the ligature cannot slip (Fig. 111). I learned this very useful bit of technic from Professor Graser, of Erlangen.

For large tumors an anterior transperitoneal incision is to be preferred over the retroperitoneal posterior lateral, especially for malignant disease. It permits careful examination of the growth, of the liver, and of the abdominal contents generally, so that the patient may not be unavailingly subjected to a formidable procedure if metastatic deposits are already present. For this reason the lungs should always be roentgenographed before deciding on operation to ascertain the presence of metastasis.

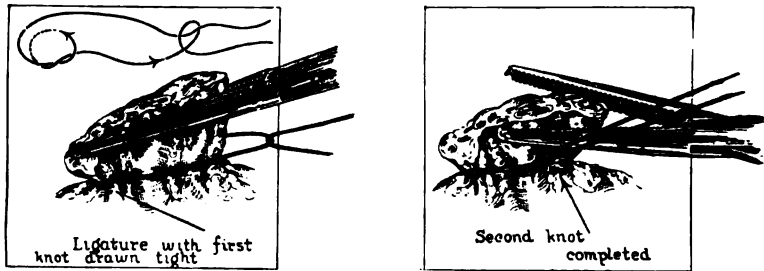


Fig. 111.—Method of ligation of pedicle (after Graser).

In malignant renal growths, if the tumor is removable, the ureter should be located at once, divided, and the ends sterilized well below the tumor to prevent squeezing infected material into the lower portion of the ureter during the enucleation. The upper end of the ureter is dissected up to the pelvis and the renal vessels secured at their origin¹ before any attempt is made to remove the growth; otherwise, polypoid projections from the tumor, which may fill the renal veins, may be forced into the vena cava. This is an accident which necropsy findings show to be not infrequent, especially in the type of solid tumor of the kidney, the renal mesothelioma (Grawitzian tumor or "hypernephroma").

III. THE MANAGEMENT OF THE URETER AFTER NEPHRECTOMY FOR TUBERCULOSIS

In our experience less than 5 per cent. of the ureters in tuberculosis of the kidney require removal. These are usually cases in which a stricture exists in the lower portion of the ureter close to the bladder, so that there is more or less retention on that side, a condition which obtains in a small percentage of the total number and which may be differentiated by ureteropyelography. Such ureters should be removed with the kidney at the primary operation.

If the kidney has become converted into a closed sac, the ureter will often be found to be obliterated just below the pelvis. In pure tuberculosis the ligation of such a ureter and sterilization of the stump disposes of it safely. In the "pipe-stem" ureters and all containing a lumen, but in which there is no mixed infection, the injection of from 5 to 10 minims of a 95 per cent. solution of phenol (carbolic acid) into the ureter, with ligation, insures such a ureter and the wound against further trouble. In these two types of cases the nephrectomy wound should not be drained, because of the danger of secondary infection of the ureteral stump which so often follows the drainage tract, leading to wound infection and sinus formation, to which I have called attention in a previous communication.⁵

Even if the wound be accidentally soiled with tuberculous material, it will be better to wipe it out carefully, fill with salt solution, and close tightly rather than to drain, if the stump of the ureter be dropped into the wound. To put it broadly, in all tuberculous kidneys which have become closed sacs or at least have lost their function, the ureter may be sterilized and dropped into the wound and in such cases the wound should be closed without drainage.

When there is secretion of urine, and especially when there is a mixed infection present, if the ureter be tied and dropped into the wound it will occasionally cause wound infection and sinus formation. If the other kidney be involved, the patient may eventually

die from phenomena having their origin in the infection. In these cases the stump of the ureter should be attached to the skin at the

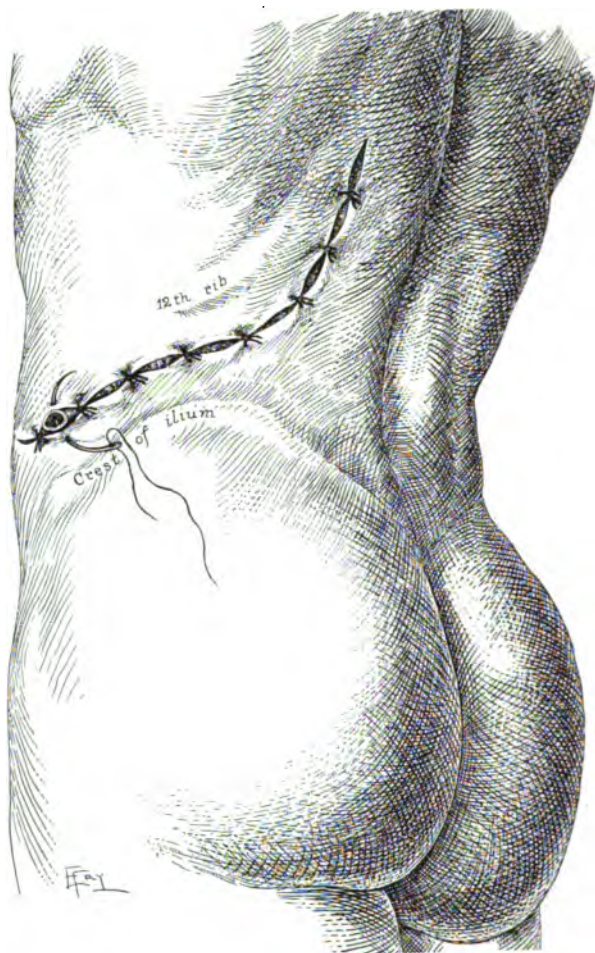


Fig. 112.—Proper incision for exposure of the kidney; ureter drawn out of anterior end of incision and sutured to skin.

anterior extremity of the incision and should not be dropped into the wound. When so attached, it permits the safe escape of discharging fluids (Fig. 112). This is especially true in recent involve-

ment of the kidney when there is considerable functioning renal tissue. The rule should be that when the kidney removed for tuberculosis is still secreting urine, if there is any evidence of mixed infection, the better practice is to attach the stump to the skin to prevent the possibility of wound infection with tuberculosis and sepsis. In just such cases the ureter will be found enlarged and softened, but not shortened or rigid.

Subsequently, the ureter will often discharge more or less for some days or even weeks, but in practically all the cases it will heal spontaneously. Those which fail to do so can be removed at a secondary operation very conveniently from in front and the removal is greatly facilitated by its anterior attachment. In a considerable number of cases in which we have attached the ureter to the skin there has been no pain or inconvenience from it beyond the necessity of wearing a little pad of absorbent material over it, should it discharge for a short time.

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FOREIGN BODIES IN THE URINARY BLADDER *

EDWARD STARR JUDD

Foreign bodies usually enter the urinary bladder through the urethra. In many of the reported cases a piece of a surgical instrument, *e. g.*, rubber catheter or dilating instrument of some kind, has been broken off or lost during the process of examination or treatment.

Packard¹ has collected and analyzed 222 cases, including one of his own, of foreign bodies introduced into the male bladder through the urethra. In 108 instances the object was a part of a surgical instrument. In the remaining 113 there was included a wide variety of articles, almost all different. The foreign body was usually introduced into the urethra purposely, then lost control of, when it slipped back through the urethra into the bladder. The length of time the objects had remained in the bladder varied greatly; in many instances it is difficult to determine just how long they have staid in the urethra before entering the bladder. In Packard's own case a piece of hard-rubber bar had been in the bladder fourteen years. Other authentic cases have been reported of foreign bodies in the bladder for at least fifteen years, and when removed, they were usually entirely surrounded by incrustations from salt deposits. Some materials, however, seem to be immune to this; in one of our cases a piece of bone had been in the bladder for some time and showed very little incrustation.

In several instances in our clinic pieces of catheters have been removed, the histories showing that they had probably been in

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the bladder for several weeks. They were usually discovered during the examination of patients for enlarged prostates or stones in the bladder, and have been removed when operating for such conditions. The following are brief histories of cases of foreign bodies in the bladder which were treated in our clinic:

CASE A19,437.—D. K., female, aged seven years. Examined January 25, 1909. The patient thought a hair-pin got into her bladder about eleven months before. Since then she has had burning on micturition (better and worse by spells), and frequency, with the passage of small amounts of urine at a time; never any hematuria. Bowels normal. Appetite good. No cramps. Urinalysis showed alkaline reaction, some pus and albumin. Roentgenogram taken elsewhere showed the hair-pin and a shadow in the area of the bladder. A cystoscopic examination was made, and a wire hair-pin embedded in the left wall of the bladder close to the urethra was discovered. The free end of the hair-pin was incrustated with a calcareous deposit. The inserted end was "S" shaped and could not be removed through a Kelly cystoscope. The child was operated on January 27, 1909, and the hair-pin, covered with stony incrustation, removed through the urethra.

CASE A73,442.—A. R., female, aged thirteen years. This patient was examined September 10, 1912. She had been troubled with enuresis since the age of nine. After exercise there was present a dull ache, referred to both loins, particularly to the right. For the past nine months there had been considerable irritability of the bladder and incontinence most of the time; no obstruction, but a great deal of urgency. Stone in the bladder was palpable per rectum. Urinalysis showed acid reaction, trace of albumin, a few red cells, and a good deal of pus. In the roentgenogram the shadow of a hair-pin, with what appeared to be a phosphatic deposit about it, showed in the vesical area. Examination with the cystoscope revealed a markedly inflamed bladder, and a large, rough phosphatic stone the size of an egg. The pin was not visible, however. It was impossible thoroughly to explore the bladder. Suprapubic cystotomy was done September 12, 1912. A large stone which formed about the pin as a nucleus was removed, and a retention catheter inserted into the urethra (Fig. 108).

CASE A112,539.—N. C., female, aged seventeen years. Examined August 10, 1914. Nothing of note in previous history except a gradual decrease in the menstrual flow for the past five

months; at the last period only a slight stain. For one year there had been urinary frequency, which was gradually getting worse. Ten months before there had been acute pain, not radiating, and lasting for several days, in the region of the right kidney. The patient was in bed three or four days. Pus but no blood was noted in the urine a day or two afterward. She had had four similar attacks since then, though during the last one the pain was not as



Fig. 113.—Hair-pin and stony deposit in the bladder, ends of the pin embedded in the wall of the bladder.

severe and of shorter duration. There had been increasing frequency and burning, with a decreasing amount of urine, occasional incontinence at night, and sometimes during the day. The urine starting and stopping by spells, was then induced to flow again by straining. Bowels constipated. Appetite fair. She said she had used a hair-pin about a year ago because she was unable to pass water. The physical examination showed hypertrophic breasts, pigmentation, and abdominal striæ suggestive of previous preg-

nancy, which the girl denied. The vagina admitted two fingers. The blood on the examining fingers was probably menstrual. The uterus was small and retroflex. Urinalysis was negative. Roentgen and cystoscopic examinations revealed a small irritable bladder; marked cystitis; one stone the size of a hen's egg, irregularly elongated, rough, phosphatic, light gray in color. A diagnosis was made of stone in the bladder, probably with a hair-



Fig. 114.—Hairpin in the bladder with stony deposit about it.

pin as a nucleus. Suprapubic cystotomy was performed under ether anesthesia August 14, 1914. The stone was removed and a tube drain inserted outside the bladder (Fig. 114).

CASE A95,006.—R. F., male, aged ten years. Examined November 5, 1913. Six hours before being brought to the clinic, November 3, 1913, this patient was shot in the abdomen with a .22 caliber rifle, the bullet striking midway between the umbilicus and the pubes. He had vomited twice and was passing bloody urine.

Pulse, 90. It was believed that the bladder and probably the intestine had been perforated. He was operated on at once, and the bullet, which had entered the bladder through the peritoneal surface, was removed. The opening was sutured with catgut and drainage inserted. The bullet had penetrated one side of a loop of the small intestine, and an ecchymotic spot was plainly visible on the opposite wall. This opening was also sutured.

CASE (Gr. Book 5, p. 432).—G. W., male, aged twenty years. Examined October 31, 1902. For the past two months there had been frequency of urination, and pain and sometimes blood at the end of micturition. The patient admitted having inserted gum into the urethra. Pus and blood were found in the urine in considerable quantities. A diagnosis was made of stone or foreign body in the bladder. November 8, 1902, a suprapubic cystotomy was done and a large piece of chewing gum with stony incrustation removed.

I wish particularly to call attention to two cases that are unique at least in some respects. In both instances the foreign body had evidently passed into the bladder through the side wall. It is of interest to note that this occurred and produced so few symptoms.

CASE A109,459.—J. M., male, aged twenty-one years. This patient came for examination July 1, 1914. Twelve years before an open jack-knife had been thrown at him, striking his left hip just posterior to the great trochanter. A large blade of the knife was broken off and never found. After the injury he was confined to his bed for three weeks. No trouble since except slight frequency by day for a long time. Twenty-one months before the examination he noted slightly increased frequency, and after two weeks for two days the urine contained a few drops of blood at the end of micturition. The winter following he passed urine about once at night and every hour during the day. In the summer of 1913 he noted smarting in the urethra after urination. One year ago, after riding horseback, all his urine was bloody for a few days. On several occasions he had noted that severe jolting caused pain in the genitalia, followed by hematuria. For several months he had had constant hematuria and pain in the urethra and perineum, the urine flowing freely at times, at others starting, stopping, and dribbling, with marked urgency. Three weeks before coming to the clinic he had had severe pain for an hour in the region of the left

hypochondrium, radiating to the back. This was accompanied by nausea. He had coughed for at least a year, sometimes expectorating mucus streaked with blood. Occasionally he had night-sweats. Weight normal. On physical examination there was tenderness per rectum, with an indefinite mass at the left, anteriorly, above the prostate. A scar on the left hip one inch long, vertical and posterior to the great trochanter, was noted. Specific gravity of urine, 1019; some albumin, a few red blood-cells, and a



Fig. 115.—Osteomyelitis of the femur. Piece of bone which has been separated lying inside the pelvic cavity. Cystoscopic examination showed the fragment of bone in the bladder.

considerable amount of pus. Examinations negative for tubercle bacilli in the sputum and urine. Roentgen and cystoscopic examinations showed a large stone in the bladder formed about a foreign body and a moderate degree of cystitis. On July 10, 1914, a cystotomy was done and a large stone formed on a knife-blade removed. The interior wall of the bladder was carefully examined, but neither wound nor scar could be found to show where the knife-blade had entered (Fig. 115).

CASE A71,701.—T. B., male, aged eighteen years. This patient was examined August 6, 1912. In 1909 he had been operated on elsewhere for the removal of a sequestrum in the region of the left os calcis. He was up and around at the end of two weeks. At that time he had a great deal of pain and tenderness in the region of the left femur. Disturbance of the bladder was first noted in February or March, 1909; pain in the bladder occurred just previous to this. He stated that some time in March, 1909, he had passed a piece of bone through the urethra, and that during 1910, 1911, and 1912 there was very often blood, sometimes clots, in his urine. In 1913 he again passed fragments of bone with the urine. There was marked atrophy of the left leg, with shortening and fixation, old sinuses of the left hip and heel, swelling in the region of the right hip, small abscess on the right forearm, and palpable cervical and inguinal glands. During 1912, 1913, and 1914 he visited the clinic several times to have plaster-of-Paris casts applied for tuberculous osteomyelitis of the left femur. When he came for consultation, the infection had already extended into the hip-joint. Roentgen and cystoscopic examinations showed the shadow of a detached piece of bone in the bladder. Tubercle bacilli could not be demonstrated either in urine or sputum. He was operated on September 23, 1914 (suprapubic cystotomy), and the piece of bone removed. Examination of the interior lining of the bladder did not reveal any scars, nor was there any clue as to how this fragment of bone, evidently a piece of sequestrum, got into the bladder. Doubtless it came from the femur, the result of the old tuberculous osteomyelitis. February 8, 1915, the patient wrote that he was feeling well and had gained 12 pounds. He notices that when he works hard there is a filamentous and string-like substance in the urine; at other times it is clear.

All the patients made uneventful recoveries (Fig. 116).

A number of instances have been reported (Freeman,² Harrison,³ Roberts⁴) in which objects have been removed from the urinary bladder that presumably had been swallowed. A case somewhat similar to those I have reported is published by Ghose,⁵ who performed a lateral cystotomy on a boy five years old and removed from his bladder a splinter of wood which had been driven into his perineum by a fall one year before.

I have been unable to find any parallel to the manner in which the fragment of bone and the knife-blade gained entrance to the

bladder. Considering the size of both, it is absolutely certain that neither of them could have entered through the urethra. They must therefore, have worked their way into the bladder through the side wall, and, according to the history of the patient's condition while this was taking place, there certainly could not have been any extravasation or leakage of the urine. Undoubtedly the foreign body was completely walled off in each case. The bladder



Fig. 116.—Large stones in the bladder formed around the blade of a knife. Blade entered the bladder through the side wall.

must have closed as quickly as the foreign body passed in. My experience with these cases has led me to believe that, in making our diagnoses, we should not rely too much on the history given by the patient, a fact clearly brought out by the roentgen and cystoscopic findings, as noted in this series of cases. Of course, the manner in which some of the foreign bodies entered the bladder is prob-

lematic, but judging from these two cases I think it may be assumed that foreign objects may pass through the prevesical tissues and the wall of the bladder into the bladder without doing any permanent injury to the wall or producing serious symptoms at the time they are passing. At least, this is the view which must be accepted until there is better proof to the contrary.

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REPAIR OF SMALL VESICOVAGINAL FISTULÆ*

CHARLES H. MAYO

The fact that vesicovaginal fistulæ are less common than formerly is undoubtedly due to better care given women during childbirth, though the condition is still occasionally seen as the result of prolonged pressure during labor. Another, or a newer, group of cases is the result of accidental or unavoidable injuries in performing hysterectomies.

Vesicovaginal fistula is a most disagreeable and troublesome infirmity because of the constant leakage, the attendant odor, and the local irritation. As seen by the surgeon, these openings, large or small, appear to be mechanically easy of closure, yet the experienced operator knows that they are often very difficult to close and that they occasionally require repeated operations. Some of the openings about the ureter and the posterior wall of the bladder with fistula leading to the vagina are best approached by the abdominal route, extraperitoneally, if possible, while the large vaginal fistulæ are best repaired by free incision and good exposure, which is often more difficult than it appears.

There are many cases in which the opening is so small as to be found with difficulty. For such and for those with a lumen not exceeding a quarter of an inch the following procedure is recommended, which I have successfully employed in a number of cases during the last twenty years. The procedure is so simple and so generally successful that it almost partakes of a "trick" operation. I am personally indebted to the late Dr. Bernays for the principle of the operation, but it was devised by Dr. R. F. Amyx, and first

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performed by him December 17, 1902. It was demonstrated to Dr. Bernays the following year (Fig. 117).

Operation.—An incision is made through the vaginal mucosa, extending completely around the fistulous opening about a quarter



Fig. 117.—a, Vesicovaginal fistula; b, inversion of vesicovaginal fistula.

of an inch or less from its margins. The vaginal mucosa is dissected toward the opening, care being taken not to break through at the margin. This makes a little cup or funnel-shaped opening projecting into the vagina. The circular dissection is carried

deeper around the fistula, not approaching nearer than one-eighth of an inch to the margin, its depth penetrating to the mucosa of the bladder, but not through it. This leaves a little bell- or funnel-shaped opening lined with mucous membrane which is connected with the mucosa of the bladder and projects into the vagina (Fig. 118). A ligature carrier is passed through the urethra into the bladder and through the fistula into the vagina. A suture is passed through both walls of the funneled mucosa on each side of the ligature car-



Fig. 118.—Separation of vesicovaginal fistula.

rier. The two ends of the silk suture are now threaded into the ligature carrier, which is withdrawn from the bladder and urethra. The ends of the suture projecting from the urethra are drawn upon, and with a little aid the fistulous tract starts inverting (Fig. 119). As soon as the mucosa disappears a circular suture of fine chromic catgut is applied, a little more traction is used on the ends of the long suture, and a second purse-string suture of catgut is applied. The vaginal side is now closed either by a circular suture of the chromic catgut

or by interrupted sutures, as seems best. This inversion turns the mucous surface into the bladder and leaves a healing surface within the tube. One of the long ends of the suture projecting from the urethra is re-threaded and by a needle is sutured to the skin of the labia. The two ends are now tied at this point, making slight traction. A self-retaining catheter (Pezzer type) is inserted into



Fig. 119.—Method of inverting fistulous tract by silk sutures.

the bladder and the patient is instructed to rest on her side or even on her face (Fig. 120). This keeps the fistulous area free from urinary pressure. After four days it is necessary carefully to watch the catheter that sediment or phosphatic deposit does not obstruct its lumen. In some cases irrigation is necessary. However, the long suture attached to the inner side of the surface of the fistula and passing through the urethra acts as a safety valve of leakage should

the catheter become temporarily plugged. After a week the repair is usually solid, but it is better to keep the patient on her side or face for a few days longer that no undue strain may be placed on the fistulous area, and during this time it is best to keep a catheter



Fig. 120.—a, Application of purse-string; b, fistula closed.

in, or if it is removed, to have regular periods for passing it. The suture from within the bladder either cuts itself out with the slight traction before it is time to remove the catheter or it may be drawn out without difficulty by cutting one side where it is attached to the skin.

THE TREATMENT BY HEAT OF ADVANCED CANCER OF THE CERVIX (PERCY'S METHOD)*

DONALD C. BALFOUR

The curability of cancer of the cervix in its early stages compares very favorably with that of cancer in any other situation in the body. Rarely, however, is the disease recognized and treated at such a favorable time; and, too often, the process is so far advanced that a radical operation cannot be done, or any treatment instituted which will offer a prospect of cure. It is unfortunate that a disease which could so easily be detected if the slight symptoms were immediately and thoroughly investigated, and which could be so favorably treated at its inception, should carry such a low percentage of operability. In this country an average of not more than 40 per cent. of these cases reaching the surgeon can be considered suitable for a radical operation. In Europe a higher percentage is claimed, the statistics of Wertheim, Schauta, Franz, and Orde showing an operability of 45 to 50 per cent. Two important factors make this true: First, the public freely consults the large centralized foreign clinics, chiefly as a result of an energetic cancer educational movement among a people whose attitude toward these free clinics is very different from that existing in this country; second, the greater the experience of the individual surgeon or clinic, the stronger the inclination to see in the borderline cases possible chances of cure, so that, other things being equal, the surgeon of the greatest experience will find the highest percentage of operability.

It is unnecessary to dwell on the familiar causes on which the

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existing low operability depends. The insidious nature of the disease, the early symptoms usually appearing at an age when the patient readily accepts the irregular flow as incident to that period of her life, absence of pain and of constitutional symptoms, and, unfortunately, often failure on the part of the physician when consulted to make a careful examination—all of these factors contribute to the infrequency with which cancer of the cervix is recognized in its early stages. To these must be added a prevalent skepticism on the part of the laity toward any operative treatment—a skepticism born chiefly of the individual's own observations of failures in the surgical treatment of advanced cancer. This attitude results in a "vicious circle"—namely, delay until malignancy is advanced; then "palliative treatment" and failure to cure; the neighbor with early symptoms is acquainted with the fact that her friend had "cancer," but not with the actual circumstances; she, therefore, has no faith in surgical measures, and tries other treatment until the curable stage has passed. Sooner or later more of the laity will realize the importance of early investigation of suspicious symptoms; and with such coöperation the surgeon will be able to extend to these patients a reasonable assurance of an increasing percentage of cures.

At the present time at least 60 per cent. of patients are apparently beyond reasonable hope of cure when first seen by a surgeon; and in fully 35 or 40 per cent. any primary radical operation is out of the question. It is this latter group of advanced cases only which will be discussed here, for I believe that cancer of the cervix in its advanced stages distinctly warrants palliative measures.

There are various resources at our command for affording such patients temporary relief—for example, the curet, cautery, acetone, zinc chlorid, and other escharotics, ligation of the blood supply, radium, etc. I have been prompted by recent personal experiences with the method advocated and developed by Percy¹ for the treatment of these "hopeless" and "inoperable" cases of cancer of the cervix to place on record my observations of this particular treatment.

For many years heat has been recognized as a very efficient

means of destroying carcinomatous tissue. Byrne² drew attention to its efficacy as a destructive agent of the cancer-cell, and since then heat has been used to a considerable extent in the treatment of cancer of various forms and stages. For many years in our clinic the cautery has been a favorite means, not only for inhibiting cancer, but it has supplanted the knife in the excision of certain circumscribed cancers, particularly of the mouth, bladder, and skin.

In advanced carcinoma of the cervix the heated soldering-iron undoubtedly has been of definite value in the amelioration of distressing symptoms of these unfortunate patients; and occasionally its use has been followed by a surprisingly long abeyance of the process. Nevertheless, I believe that the modification which Percy has developed, if properly carried out, offers the best opportunity for the destructive action of the heat to reach the limits of the disease, and that it possesses distinct advantages over any other form of treatment with which we are familiar.

At first the application of this method was restricted to the most advanced cases; but of late its unique destructive effect becoming evident, the scope of the treatment has extended, and it has been employed as the primary stage to a secondary total hysterectomy in an occasional so-called "border-line" case. In discussing the advisability of any treatment for advanced malignancy of the cervix, the patient or her family should clearly understand the seriousness of the condition; and they should especially appreciate the purpose of the treatment. In apparently hopeless cases it should be carefully explained that the object of surgery is to relieve whatever distressing symptoms may be present and prolong life. Perhaps in no other instance of advanced malignancy is one able to offer such decided retardation of the progress of the disease and such complete relief of symptoms. In those cases in which a primary radical operation is not possible, but in which a total hysterectomy may be advisable later, it is important to have this understood.

Briefly, the basis from which this treatment has been evolved depends upon the fact that a slow-heating process is much more efficacious in such conditions than a vigorous burning. In his

various articles on the subject Percy has shown quite conclusively by experiment that heat will permeate living tissue much more readily and effectively if maintained at a comparatively low degree for a long time than if a high degree is maintained for a short time. Referring to certain advantages in the instruments devised by Percy, and in the application of the method, I should say that— (1) One may obtain the best possible exposure of the disease without incision by means of the vaginal dilator; (2) the water-cooled speculum permits uninterrupted heating of the malignant area without the danger of burning uninvolved vaginal walls or external genitals; (3) the preliminary abdominal exploration often discloses important findings; (4) the hand of the assistant used as a guide to the degree of heat, directs the point of the cautery and at the same time supports the cervix and protects the bladder and rectum. Accurate and occasionally valuable information as to the extent of involvement, condition of the glands, etc., is thus obtained; and the assistant, through the low midline incision, is able to give helpful advice as to the intelligent application of the heat. The treatment is practically free from risk; patients are up on the fifth or sixth day; convalescence is remarkably comfortable; and any pain which may result is associated with the abdominal incision, and is not incident to the heating.

As yet I cannot speak of any save immediate results, since we have used the method only from January 1, 1914, to the present time (May, 1915). In that period 31 cases of cervical carcinoma, which were too far advanced to permit primary radical operation, have been treated. Certain beneficial results have already become quite evident in this series. In all there has been cessation of bleeding and discharge immediately following the treatment, with a corresponding improvement in the general condition, an improvement, of course, particularly striking where bleeding, sepsis, and absorption had gone on to the point of emaciation. We have been fortunate in being able to closely follow the results of the treatment, the majority of patients returning for examination in six weeks to three months; and we have repeatedly noted the unique change which has taken place in the local manifestations of the

disease in these patients. To find at this reëxamination a freely movable uterus, with an atrophic, smooth, clean cervix and vaginal vault, is not uncommon. Patients in whom gross evidence of the disease exists after a thorough initial treatment have not, except in a few instances, seemed to be suitable for a secondary treatment; but sufficient time has not yet elapsed for conditions indicating repetition of the treatment to develop.

With our present limited knowledge of the scope of the treatment, I believe that, regardless of how favorable the result may appear to be, if it becomes technically possible and of sufficient promise and no logical contraindications are present, a secondary total hysterectomy should be done. Of the patients treated by the method in our clinic, a secondary hysterectomy has been performed in nine. It is important to note that in five of these cases subjected to the radical operation, the pathologist, in careful search of the specimens, has not been able to demonstrate any evidence of malignancy. Despite this, and although malignancy may be destroyed as far as can be determined, with our uncertain information as to the life-history of cancer, it seems more rational to consider such a uterus potentially malignant.

It is possible that in some of the patients in whom the cautery was used, and who later had a total hysterectomy, a primary hysterectomy would have been possible. We have found, however, that in border-line cases a preliminary heating process is of undeniable value in increasing ultimate chances of getting rid of the disease. The destruction of the cancer-cell is not the only advantage; in from two to three months a shriveled cervix in a scarred, firm vaginal vault makes it possible to do a much cleaner and more satisfactory operation from a technical standpoint. The foul, infected tissues of the cancerous cervix are sterilized, making the operation less exposed to septic complications. In this connection it is interesting to note that the favorable, immediate, and, possibly, ultimate result may depend to a considerable extent on the destruction of the infected, non-malignant portion of the disease, whatever the organism may be. When it is realized that of those persons dying from cancer of the cervix a relatively small percentage show

any evidence of metastasis, the disease, being still a strictly local one at the time of death, the rôle of the bacterial infection becomes an important one.

Percy's writings and technic have been followed as closely as possible in carrying out the method in our clinic. The complications have been vesical fistulæ, late secondary hemorrhage, and vaginal grafting. The autogenous grafting of cancer may readily occur, as, in the great stretching of the vagina, cells may become implanted in the fissures in the walls. We have had three cases in which secondary malignancy developed at the vulva. This should be prevented by introducing into the vagina several ounces of Harrington's solution as the speculum is withdrawn, so that the fissures will be rendered unsuitable soil for such grafting, and any fresh cancer-cells present will be destroyed. In two cases vesico-vaginal fistulæ resulted from the treatment; but it is significant that these occurred in our earlier experiences. In both patients a total hysterectomy had been done, recurrence having taken place in the vaginal vault with fixation to the bladder. At this time we were neglecting the precaution of opening the abdomen. Since these experiences the abdomen has been opened routinely. Danger of secondary hemorrhage will be minimized if the heating is thoroughly carried out for a sufficient length of time, and the internal iliac arteries are ligated in the more advanced cases.

The electric cautery should not be used to the point of cauterization, but as a heating instrument only. This is a most important factor in the treatment. The rheostat should be regulated so there is never any charring of the tissues, since this acts as an asbestos covering, preventing penetration of the heat, but rather a slow-heating or cooking process should be continued until the assistant's gloved hand within the pelvis grasping the cervix and uterine body is made uncomfortably hot (120° F.). It has been shown experimentally that this degree of heat is sufficient to kill any cancer-cells. An hour or more is often necessary to accomplish the desired object and to systematically heat all the segments of the carcinomatous mass. This treatment requires patience, especially after one has been accustomed to the rapid method of cauterization

with soldering-irons; but, I believe, the results more than compensate for the time expended and the results are more or less directly dependent upon the earnestness of the effort.

I hope later to publish more definite results and details of individual cases; but in the meantime I desire to draw attention to the method as one worthy of conscientious trial.

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THE RELATIVE MERITS OF THE OPERATIONS FOR CANCER OF THE UTERUS *

DONALD C. BALFOUR

The best operation for cancer of the uterus is the one which permits the widest extirpation of the disease commensurate with the lowest possible operative mortality, and the minimization of immediate and late complications. Unfortunately, no one operation has proved so satisfactory, either in primary or ultimate results, as to leave the treatment of cancer of the uterus on a settled basis. Certain peculiar features of cancer of the uterus, and particularly of the cervix, in relation to symptomatology, variability in malignancy, and the rôle played by infection renders important the intelligent utilization of every known means to combat the disease.

Unless further evidence is more convincing, it is safe to assert that, regardless of the efficacy of any treatment of the cancer *in situ*, an organ in which cancer has developed should be removed, if such organ is of itself not essential to life. There can be no logical argument that the general surgical principles accepted in the treatment of cancer in other regions should fail to be applicable to cancer of the uterus. It is true that in cancer of the cervix its anatomical relationship to the bladder, ureters, and rectum and its relative inaccessibility introduces problems which alone tend to limit efforts toward its treatment.

It is well known that with cancer in any part of the body, secondary infection is an important factor in the spread of the disease, and consequently in the immediate and end-results of the opera-

* Presented in the symposium on Cancer of the Uterus, at the meeting of the Clinical Congress of Surgeons of North America. Reprinted from Surg., Gyn. and Obstet., 1916, xxii, 74-79.

tion. Malignant disease of the cervix is a good example of this septic type of cancer, statistics showing that in 40 per cent. of persons dying from cervical cancer no evidence of metastasis is found. The infection, as shown by Rosenow, is usually streptococcic, and any surgical measure which does not at the same time sterilize the growth and the surrounding tissues is open to serious objection. A study of the results following the older types of operations for cancer in any septic situation shows a high relative mortality from the disease, depending as much on the degree of infection as on any other factor, and herein lies the justification for the clinical belief in the use of the actual cautery.

Much of the pessimism in regard to the earlier history of operations for cancer of the cervix was due to the fact that the disease was often disseminated as a direct result of the traumatism of the operation, not only through the vascular system and the lymphatics, but by transplantation to the operative wound. Autogenous grafting as the result of mechanical injury is an important cause of recurrence and is frequently observed in cancer in various situations. This possibility must always be borne in mind in carrying out any operation for cancer. Undoubtedly recurrences have taken place, particularly in dealing with cancers of the cervix, from failure to recognize this fact, the recurrence being due not to incomplete removal of the disease, but rather to the engrafting of cancer-cells on cut and lacerated surfaces.

Of the various operations for cancer of the uterus, there is no doubt that total abdominal hysterectomy, as popularized by Wertheim, is the most radical surgical procedure we possess for dealing with the disease, and no method gives higher percentages of permanent cures, especially if preceded by cautery sterilization of the primary lesion. One must, however, give serious consideration to certain indisputable facts associated with this operation. The primary mortality is higher (Wertheim reports 19 per cent.) than in any other method; immediate complications, such as ureteral and other fistulæ, are relatively frequent (Wertheim reports 7 per cent.), while late complications, such as pyonephrosis, are not rare. It is possible that this primary mortality can eventu-

ally be reduced to less than 10 per cent. by improvement in surgical technic. The possibility of fistulæ of the bladder, rectum, ureter, etc., can also be greatly minimized, especially if the practice is followed of completely or nearly closing the abdominal cavity and not packing the pelvis with gauze brought out through the vagina. Since we have discontinued the use of gauze in actual contact with the possibly injured ureter, or bladder, etc., fistulæ have not developed.

Do the late results justify an operation which is so extensive in its glandular dissection that serious sequelæ are possible, to say nothing of the initial high mortality? It would seem, from our own statistics, that in the average case they do not, and that some modification of the Wertheim operation will give as good results with less risk.

A study of our statistics shows that the results of vaginal hysterectomy for cancer of the cervix by the old bloody methods seldom permanently cured the patient and that when the clamp and cautery method was introduced about fifteen years ago, there was a marked change for the better, in ultimate results, with an operative mortality well under 5 per cent. A brief description of the operation as done in our clinic may not be amiss.

The cancer, when situated in the cervix, is first destroyed by the cautery, and then a dissection made with the Paquelin cautery knife through the vagina and perimetrial tissues, the separation of the bladder by gauze dissection being the only part of the operation which is not done with the cautery. If the fundus of the uterus is drawn out anteriorly before clamps are placed and the clamps applied from above down, injuries to the bladder and ureter do not occur. After removing the uterus in this manner, the tissues in the bite of the clamps and the clamps themselves are thoroughly heated. The clamps are left on forty-eight hours and unlocked at least ten hours before removal. The iodoform gauze which has been packed lightly into the space between the clamps is left undisturbed for six or seven days. This operation has given as good results under similar conditions as have been obtained from total abdominal hysterectomy and with a lower operative mortality.

It is especially applicable to elderly and obese patients and to those who, for any other reason, are poor surgical risks.

The development of cancer may be described as progressive transplantation into the tissues. Experimentally, it has been shown that cancer-cells are less resistant to heat than normal cells and that heat prevents successful transplantation; therefore the tissues to as great a distance as possible from the local lesion should be heated to a point which will prevent the progress of the disease. The heat must be applied slowly for at least one hour.

Percy has developed a method which derives the full value of this agent in the treatment of cancer of the cervix. I became interested in this method about two years ago, and from experience in more than one hundred cases am convinced of its great value. Its essential and advantageous features are: (1) The slow heating process; (2) the abdomen always open; (3) the gloved hand of an assistant in the abdomen indicating the effectiveness of the heating process, and (4) the water-cooled speculum. The method undoubtedly offers more to the patient with advanced cancer of the cervix than any treatment with which we are familiar. Its value is so definite in the advanced stages that serious consideration must be given its possibilities in the earlier stages of the disease.

Recently, in several of our cases of advanced cancer of the cervix, the Percy treatment has been accompanied by ligation of both internal iliacs. The ultimate benefits of this procedure cannot yet be foretold. Attention should be drawn to the fact that in stretching the vaginal tissues in order to use large specula, secondary carcinomatous nodules may develop in the vagina and about the vulva. This occurred in four of our cases, evidently due to transplantation into fissures produced by the stretching. We are now careful, after any operation through the vagina, to remove any particles by irrigation and then swab out the vagina and fissures with Harrington's solution or tincture of iodine to discourage the occurrence of such unnecessary and unfortunate sequelæ.

For the moderately advanced cancer of the cervix, the advantages of a two-stage operation have gradually become apparent.

First, treatment by heat (Percy method), as in the inoperable cases, and conducted as though no further operation would be necessary; second, a total abdominal hysterectomy some weeks later. It has been interesting to note that of 16 such patients operated on in our clinic, although in three cancer-cells were still present, in 13 there were no macroscopic or microscopic evidences of the original disease. Regardless of this fact, other things being equal, I believe that the uterus should be removed. Although the results following the clamp and cautery operation were relatively excellent, the two-stage operation offers distinct advantages and we are employing it more and more frequently. For cancer of the body of the uterus total abdominal hysterectomy is the operation of choice; vaginal hysterectomy being employed only when, because of the poor surgical risk, such a route possesses positive factors of safety.

In the so-called "inoperable" cases, heat with ligation of the blood-supply limits the progress of the disease, stops bleeding and discharge, improves the patients' health temporarily, and occasionally converts what is apparently quite a hopeless inoperable condition into an operable condition. Our experience with the Coolidge tube and with radium has not been sufficient to justify an opinion as to the permanency of cure, but in the few cases observed, extraordinary benefit has been derived.

Summary of the present status of operative procedures for cancer of the uterus in our clinic:

1. Patients with cancer of the cervix not too far advanced and who are good surgical risks should be treated by thorough cautery sterilization of the local disease in the cervix, and total abdominal hysterectomy of the Wertheim type.
2. When cancer is confined to the cervix, the vaginal outlet fairly lax, and the patient is a poor surgical risk, *i. e.*, obese, with cardiorenal disease, etc., the preferred treatment is the clamp and cautery vaginal hysterectomy.
3. In the more advanced stages of the disease, if the patient is a good surgical risk, the two-stage operation should be done, *i. e.*, the Percy method of tissue coagulation by heat, followed after some weeks by total abdominal hysterectomy. If the patient is

a poor surgical risk the Percy method should be applied, but the abdominal hysterectomy should be considered on its merits in the individual case.

4. In most instances in cancer of the body of the uterus a total abdominal hysterectomy should be done. In the small minority of patients with cancer of the body of the uterus who are poor surgical risks, clamp and cautery vaginal hysterectomy may be indicated.

The foregoing observations are based on a review of 634 cases of cancer of the uterus operated on in our clinic during the past ten years. A detailed history of these, with the ultimate results, will be published later.

DUCTLESS GLANDS

THE ISOLATION IN CRYSTALLINE FORM OF THE COMPOUND CONTAINING IODIN WHICH OCCURS IN THE THYROID; ITS CHEMICAL NATURE AND PHYSIOLOGIC ACTIVITY *

EDWARD C. KENDALL

Previous investigation has shown that the thyroid exerts marked physiologic activity when administered to the normal animal and man, and that the removal of the gland is followed by profound changes. The extremes of thyroid disturbance are seen in the two syndromes, exophthalmic goiter and myxedema. Between these extremes are many indefinite or border-line conditions, so that thyroid disturbances present a confusing mass of evidence which is not easily diagnosed or classified. Clinically, the cases have been classified and a basis of diagnosis established. Much light has been thrown on the progress of the disease of exophthalmic goiter, and the physiologic properties of the toxic substance responsible for the symptoms have been described (Plummer¹).

From clinical observations the thyroid has been supposed to have a secretion which contains a substance or substances capable of producing certain physiologic activity. But the acceptance of such a theory in itself erects a barrier beyond which the clinician cannot go. The only passage of that barrier is a method which will unlock the constituents of the thyroid secretion and separate the active substances in pure form. Definite conclusions cannot be

* From the laboratories of St. Luke's Hospital, New York, and the Mayo Clinic, Rochester, Minnesota. Reprinted from the *Trans. of the Association of Amer. Physicians*, 1915.

arrived at as long as these substances are known only by the symptoms produced by their presence or absence (Wilson²).*

What is the substance in the thyroid that produces toxic symptoms? What is the relation of iodine to thyroid activity? Is the iodine in the gland present in a hitherto unknown substance specific for the thyroid? What is the compound in the thyroid essential for normal life? Does the thyroid secretion contain more than one active constituent? Can the active substance or substances be separated from the gland in pure form and retain their activity? These and many more problems can be answered only by separation in pure forms of the substances in question, and by investigation of their physiologic activity.

Attempts to isolate the active principle have resulted in preparations which may be divided into two classes: (1) Those secured by separation of products of protein nature without decomposition or destruction of the protein molecule, and (2) those obtained by means of hydrolysis of the protein and the subsequent separation of the decomposition products. In the first class of preparations are Oswald's³ thyroglobulin and iodine-free nucleoprotein. Other investigators have prepared similar proteins from the thyroid. These products, which are original protein compounds unchanged in chemical nature, still retain their activity, as shown in the treatment of symptoms of cretinism and myxedema. In the second class of preparations, Baumann's⁴ iodothyron, containing about 9 per cent. of iodine, is the result of decomposition of the proteins with sulphuric acid. The iodothyron so obtained is about 4 per cent. of the total weight of the dried thyroid. Other decomposition products have been obtained by Hutchinson⁵ working with pepsin and trypsin on the thyroid proteins. Hutchinson separated in this way a product containing 3.6 per cent. of iodine.

Another means of throwing light on the nature of the iodine compound has been to prepare various iodine compounds and test the physiologic activity of these. Di-iodotyrosine, tetra-iodohistidine,

* No comprehensive review of the clinical and pathologic aspects of thyroid disturbance is attempted in this paper. For discussion of these and a presentation of the views held in our clinic reference is made to Wilson's article under reference 2.

tri-iodo-imidazol, iodized tryptophan, and iodized phenylalanin and other organic compounds have been tested in this way, but no compound has been found which produces effects similar to those of desiccated thyroid.

This paper contains a summary of an investigation of the chemical constituents of the thyroid, which has been carried on during the past six years. The object of the work was to isolate in pure form one or more chemical compounds which possess physiologic activity.

Dialysis was used as a preliminary study of the proteins of the gland and the nature of iodine combination. Desiccated thyroid, either in suspension or dissolved in dilute alkali, was found to lose less than 5 per cent. of its total iodine by dialysis in a collodion sac against running water. Experiments were then made, varying the temperature and acidity of the dialysate. These results showed that increase in temperature and acidity favored dialysis of the iodine compound, and as much as 40 per cent. could be made to pass through the sac in this way. Attempts were then made to alter the nature of the proteins to see the attending influence on dialysis of the iodine. Boiling in strong sodium hydroxid allowed 80 per cent. of the iodine to pass the dialyzing sac. Boiling with sodium hydroxid and hydrogen dioxid allowed 90 per cent. to pass.

These results showed a decomposition of the protein and a probable splitting off of iodine in the inorganic form. As such vigorous treatment would undoubtedly destroy physiologic activity, further experiments were conducted to find some treatment which would break down the complex proteins into simpler products without destruction of the compounds so obtained. Alcohol was tried as a medium for the carrying out of such treatment. Alcohol saturated with hydrochloric acid gas was tried as a hydrolytic agent, but no satisfactory cleavage resulted from its use. Hydrolysis with sodium hydroxid in alcohol was then tried, and it was found that this method produced a cleavage different from any of the others. Seventy-five per cent. of the iodine was dialyzable, but it was easily shown that the iodine was not split off as sodium iodid, but still existed in organic combination. After it was shown that sodium

hydroxid in alcohol altered the nature of the protein to a marked degree, dialysis, as a criterion of the nature of the iodine combination, was discontinued, and a detailed study of the chemical properties of these products of hydrolysis was begun.

No specific precipitant was found for the iodine compound in either an alcoholic or aqueous solution. After many attempts to find such a reagent it became apparent that the iodine was present in two different forms of organic combination. About 50 per cent. of the total iodine was soluble in acid and 50 per cent. was insoluble. As the solubility in acids effected a separation between the two apparently different iodine compounds, this treatment was used as the first step in the separation of the products of hydrolysis. Those compounds insoluble in acid are designated constituents of Group A, and those soluble, constituents of Group B.

All the constituents of Group B are easily dialyzable. Saturation of a solution of B with ammonium sulphate produces a sticky, tarry precipitate which evidently consists of amino-acid complexes and carries down with it about 80 per cent. of the iodine in B, showing that it is still present in organic combination.

The iodine compound in B is precipitated to a large extent with mercury sulphate, and almost quantitatively with silver sulphate in the presence of magnesium oxid. A large percentage of the iodine is split off by this treatment. Oxidizing agents, even copper acetate, also easily split off the iodine from its organic combination.

After establishing the general chemical properties of Group B, efforts were directed to a more extended study of Group A. The most striking chemical property of A is its acidic nature. All the constituents of A are easily soluble in dilute alkali or ammonia, and are reprecipitated by any acid stronger than carbonic acid.

Experiments with organic solvents showed that uncombined sulphur, fatty acids, and about 10 per cent. of the iodine in A is soluble in ether. The fatty acids doubtless came from the fats which were saponified by the alkaline alcohol and the sulphur probably resulted from the decomposition of cystin. Further experiments showed that the solubility of the iodine in organic solvents varies greatly, it being least soluble in petroleum ether. The sec-

ond step, therefore, for the purification of A is the removal of fatty acids and sulphur by extraction with petroleum ether. The product thus obtained contains about 4 per cent. of iodine, and this preparation may be dissolved in alkali and reprecipitated with acids without appreciable loss of its total iodine. This treatment slowly removes some constituents containing nitrogen but no iodine, so that the percentage of iodine in A may thus be increased to about 6 per cent.

This preparation is a dark-brown powder, insoluble in water and acids, easily soluble in dilute alkali and ammonia. Its alkaline solution is precipitated by copper hydroxide and to a large extent by barium, calcium, and magnesium salts. It is almost entirely soluble in ethyl acetate, but by partial extraction with this solvent it is possible to separate A into two fractions. In the ethyl acetate soluble portion of A the percentage of iodine may be increased to 13 or 14 per cent., the ethyl acetate insoluble fraction containing only 1.5 per cent. iodine.

Except for the solubility in ether, the general chemical properties of A closely resemble those of a fatty acid. By further hydrolysis of the A group the compound containing iodine has been separated in pure crystalline form. The details of this separation will not be given at this time, but the reactions upon which the method is based are as follows: (1) The compound is stable in the presence of sodium hydroxide in aqueous and alcoholic solutions; (2) it is exceedingly insoluble in all acids, including carbonic acid; (3) its barium salt is soluble, which gives a separation from fatty acids and other impurities; (4) it is insoluble in alcohol in the presence of sodium acetate; (5) it may be precipitated by boiling its ammoniacal solutions. Its exact formula cannot now be stated, but it appears to be di-iodo-indole carboxylic acid. It crystallizes in microscopic needles that melt at about 220° C. It is very insoluble in alcohol, ether, water, acids, and sodium carbonate. Dilute hydrochloric acid dissolved 1 part in about 200,000. It is readily soluble in dilute alkali and ammonia (Fig. 121).

The thyroid having been separated into several different constituents, it seemed desirable to test each one for its possible

physiologic activity. These preparations were first tested with normal dogs kept in metabolism cages. Administration of Group B constituents by mouth or by subcutaneous or intravenous injection

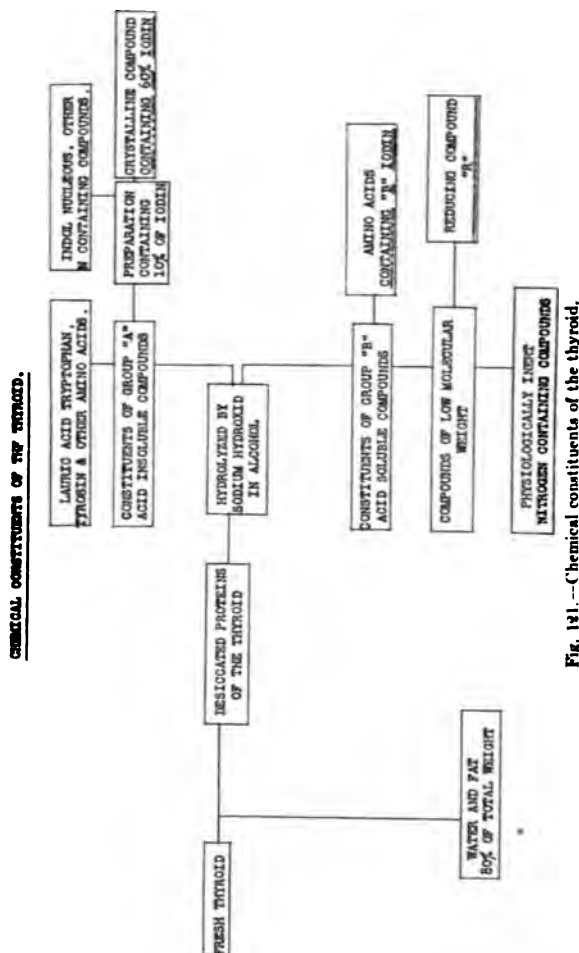


Fig. 181.—Chemical constituents of the thyroid.

tion produced no apparent effect on the temperature, blood-pressure, pulse-rate, nitrogen balance, or weight. Administration of Group A constituents by mouth or subcutaneous injection produced the typical so-called hyperthyroid symptoms: increase in pulse-

rate, slight increase in temperature, marked increase in nitrogen elimination, with loss of weight, increase in nervous irritability, and tremor.

These results showed that the toxic symptoms following administration of the gland can be produced by a small group of constituents which amount to only 4 to 5 per cent. by weight of the desiccated thyroid.

Further investigations concerning the injection of Group A constituents were carried out on a large number of dogs under varying conditions. A typical result is as follows: Weight of dog, 10 kilos; pulse-rate during previous ten days, 90; 200 mgm. of A used for each injection. Following the injection there is no immediate effect on the temperature, pulse-rate, or blood-pressure, and twenty-four hours after the injection there is still no apparent change. The substance injected seems to be inert, but at this time another injection of 200 mgm. is given and the observations continued. From thirty-six to forty-eight hours after the first injection the dog appears restless, the temperature is slightly increased, and the pulse-rate has reached 120. The observations and daily injections are continued. On the fourth or fifth day the dog is in a highly nervous condition, restless, with tremor, and there is generally severe diarrhea; the pulse-rate is between 200 and 250. Beside the high rate, the pulse has changed its character, becoming hard and hammer-like, with spasms of tachycardia. Although the daily injections are continued at this time, the dog rapidly becomes better, the pulse-rate decreases to about 120, and the hard, pounding effect disappears. If the injections are now stopped, the dog returns to normal, the pulse-rate even dropping to 68 to 70 in some cases.

NATURE OF THE TOXIC COMPOUND.—Having shown that toxic effects are produced by a certain group of constituents of the thyroid, attempts were made to determine the chemical nature and to isolate in pure form the toxic substance contained in this group of compounds.

The presence of iodine as a normal constituent of the thyroid has been known for twenty years.⁴ During this time many contro-

versies have arisen out of attempts to explain the relation between the physiologic activity and the presence of iodine.^{7, 8, 9, 10, 11, 12, 13} From the beginning of this investigation the isolation of the compound containing iodine was held as the main objective, hence the iodine content of the various preparations of the A constituents was always determined.

By the use of A made from beef, hog, sheep, and pathologic human thyroid it was readily shown that the toxicity of A is directly proportional to its iodine content. By extracting A, containing about 5 per cent. of iodine, with ethyl acetate, it was fractionated into two parts: one containing about 9 per cent. of iodine and the other 1.5 per cent.; but, taking iodine as the standard and the effect on the pulse-rate as the criterion, both these preparations produced toxic effects. This indicated that the active substance in each case was the compound containing iodine, and that this substance was combined differently in the two preparations.

The toxic effects of A were first produced by preparations containing from 4 to 5 per cent. of iodine. Later the A constituents were further broken down and a purer form, containing 25 per cent. iodine, was obtained. Injection of this under the same conditions, using iodine as the standard, produced the typical effects.

Finally, the iodine-containing compound was isolated in pure crystalline form having a constant iodine content of 60 per cent. These pure white crystals, used in amount equivalent to previous injections, keeping A iodine as the standard, produced the typical symptoms with the same severity. We can, therefore, conclude that the substance in the thyroid responsible for the production of toxic symptoms is the compound containing A iodine, and that this compound can be separated in pure crystalline form without loss of its activity (Fig. 122).

To determine whether the sudden improvement in the general condition following a series of injections of A resulted from the development of a tolerance to the A compound, a dog was injected until in a highly toxic condition, and was then allowed to return to normal. To a second dog two series of injections were given, the second series being precisely similar to the first. Under the effect

of the second series the dog lost weight, had severe diarrhea, became nervous, and appeared to react as severely as during the first series, except in regard to the pulse-rate. At no time was the rate as high, and it did not develop the hard, pounding property to such a degree. The other symptoms followed much the same course as during the first series. To a third dog three series of injections were given, the previous conditions being observed. Again, the dog reacted as



Fig. 122.—Crystals of the iodin-containing compound which occurs in the thyroid.

before, but after the third series appeared less capable of throwing off the toxic effects. While the pulse-rate was not high, there were spasms of tachycardia when the rate reached 280 to 300; but when quiet and not under excitement, the rate was about 150.

These and other results indicate that the A iodin compound does not work in a rapid and direct manner, and that some form of tolerance is produced. Further experiments are being carried out to explain more fully the factors involved.

THERAPEUTIC EFFECTS OF A AND B IN MAN.—The physiologic results on dogs established the general toxicity of A and the non-toxic effect of B sufficiently to warrant the use of these preparations for therapeutic purposes in cases of thyroid disturbance, and during the past three years many patients have been treated.

As repeated injections over long periods are impracticable in man, the split products were always given by mouth. The results obtained may be briefly stated to be entirely in accord with the preliminary tests on dogs. No toxic effects have ever been produced by the B constituents, although more than 200 patients have been treated; but the A constituents, even in small amounts, produce toxic effects.

The severity of the toxic effects following administration of A to normal individuals varies greatly, but in general it is as follows: If to a normal individual with a pulse-rate of about 75 and a weight of about 75 kilos sufficient A is given per day to contain 3 mgm. of A iodine, on the day following the first dose there is no apparent change except a slightly increased pulse-rate. If the same daily dose is continued, the patient slowly reacts, and in the course of eight or ten days nervous symptoms develop, the pulse-rate is around 130 to 140, there is a tendency to perspire more freely on exertion, and the patient may be short of breath and easily tired. At first there is an increased appetite, but later loss of appetite, nausea, and sometimes diarrhea develop. During this time the patient usually loses weight—from 1 to 5 kilos (idiosyncrasy?). If smaller doses are given, the severity and course of symptoms are modified, but the patient will react to very small amounts of A. If large doses are given, there results a serious condition in which the above symptoms are exaggerated.

As in the tests on animals, the therapeutic results on the human being were first obtained with preparations of A containing about 4 to 5 per cent. of iodine. Later they were repeated, using the purer form of the compound that contained 25 per cent. of iodine, and, finally, the typical effects with the same severity were obtained by using the pure crystalline compound containing 60 per cent. of iodine.

These results brought out a great difference in the sensitiveness of dog and man to the toxic iodin compound. To produce effects in dogs, about 1 mgm. of A iodin per kilogram weight of dog is required for a daily dose. In the human being severe symptoms follow the administration of as little as $\frac{1}{5}$ to $\frac{1}{2}$ of 1 mgm. per body weight per day. Furthermore, the nervous system seems to respond much more quickly and strongly in the human being than in the dog. Why the minimum dose required to produce toxic effects in people varies greatly is now being investigated.

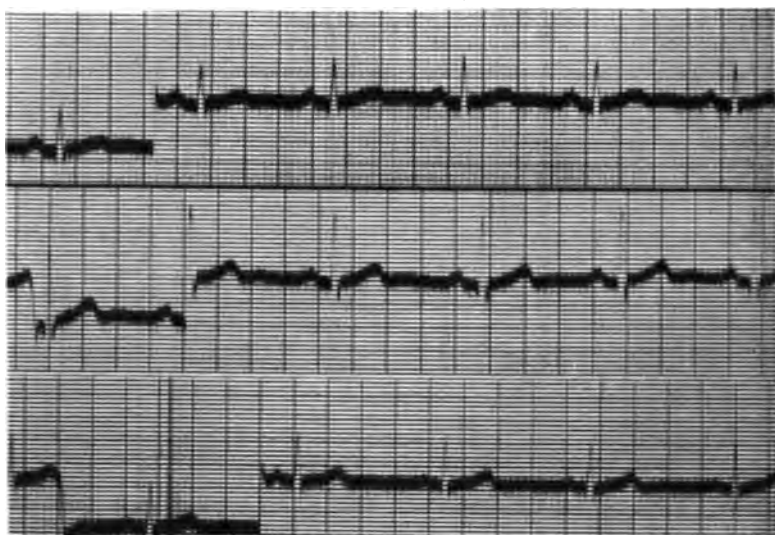


Fig. 123.—Cardiogram of normal man on entering clinic. Pulse-rate, 75. Body resistance: first lead, 5000 ohms; second lead, 7000 ohms; third lead, 7000 ohms.

In this connection it is interesting to recall the argument put forward that the iodin compound in the thyroid was not necessary for physiologic activity, as the thyroid of the fetus and infants contains little or no iodin,^{13, 14} a point which has been well reviewed by Hunt.⁷ Fenger¹⁵ has recently shown that, with proper technic, the presence of iodin can be demonstrated in the thyroid of the fetus, and the results reported in this paper show why so little is present. If a daily dose of $\frac{1}{4}$ of 1 mgm. is too much for a seven-year-old

cretin weighing 20 kilos, it is readily seen that the thyroid of a 3 to 5 kilos fetus need not contain a very large amount of iodine to maintain the normal function of the gland.

In addition to observations on the pulse-rate and general condition, electrocardiograms were taken of several cases. The results obtained were very marked and surprising, and while the number of cases is not large, they seem to justify a preliminary report at this time.

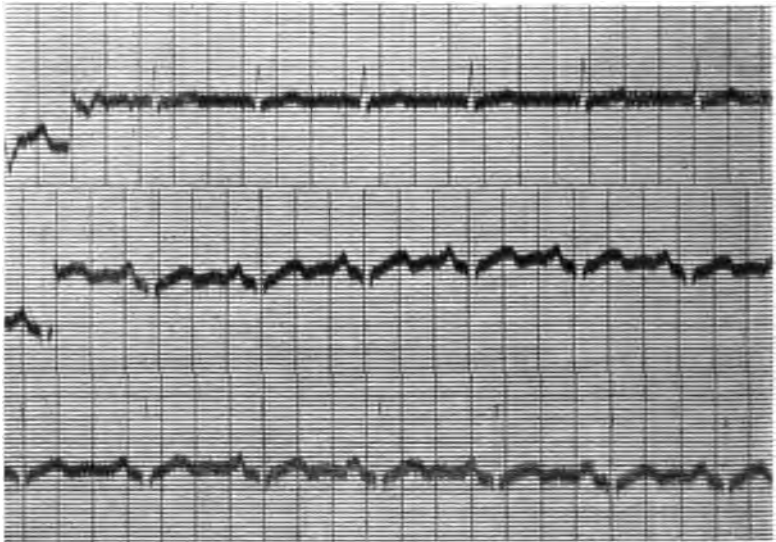


Fig. 124.—Cardiogram of same patient after taking A-iodin for two days. Daily dose, 3 mgm. Pulse-rate, 90. Body resistance: first lead, 6900 ohms; second lead, 5900 ohms; third lead, 6900 ohms.

In every case there was a change which appeared by slow and regular steps, so that a series taken on fourteen or twenty-one successive days showed a great difference between the first and last, but the change between any two days was hardly noticeable.

The following three cardiograms shown were taken with the fiber standardized to such a tension that 1 millivolt tension produced a change of 1 cm., the patient being in circuit. The resistance of the patient was determined in every case. These three cardiograms, which are from a series of 18 taken on successive days, indicate that

still, under these conditions, there are changes in the various waves of the cardiogram as well as in the pulse-rate. A more detailed study of these changes is now being carried out (Figs. 123, 124, and 125).

EFFECT OF A AND B ON GROWTH AND MENTAL ACTIVITY.—It has long been known that the growth of cretins is materially influenced by administration of desiccated thyroid. It was therefore interesting to determine the effects of A and B in this respect. A cretin, aged nine years, weight 16.8 kilos, height 93 cm., was given

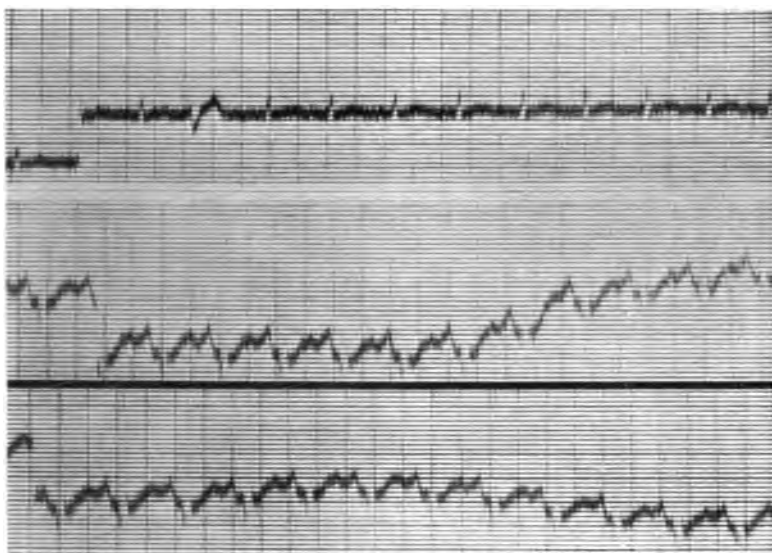


Fig. 125.—Cardiogram of same patient after taking A-iodin for two weeks. Total amount taken, 61 mgm. Pulse-rate, 144. Body resistance: first lead, 2250 ohms; second lead, 2500 ohms; third lead, 1250 ohms.

B alone for ten weeks. Observations on her pulse-rate, weight, and height showed no appreciable change during this period, although certain other conditions, which are discussed later, were relieved. At the end of the ten weeks a small amount of A (0.5 mgm. A-iodin) was included in the daily dose. As there was a rapid response, the pulse-rate increasing to 140, the dose was reduced to $\frac{1}{3}$ mgm. of A-iodin per day, and this amount was continued for six months. Her weight and height were taken on the following dates:

Dates	Weight kilos	Height cm.
January, 4, 1915.....	16.30	92.5*
January 27, 1915.....	16.10	95.0
February 27, 1915.....	16.70	95.0
April 2, 1915.....	17.30	97.5
May 5, 1915.....	16.90	97.5
June 24, 1915.....	17.10	99.5
July 8, 1915.....	18.60	102.0



Fig. 126.—Cretin as she appeared on entering Clinic. Patient had never been treated with any thyroid preparation. Aged nine years; height, 93 cm.; weight, 17.3 kilos.



Fig. 127.—See Fig. 126.

* The observations on January 4 and July 8 were taken at our clinic. The other measurements were made at the home of the patient.

Although no apparent effect was produced with the B constituents in respect to growth, administration of A-iodin was followed by



Fig. 128.—Same patient eight months after Fig. 126. During this time patient was given the A-iodin compound. Height, 102 cm.; weight, 18.6 kilos.



Fig. 129.—See Fig. 128.

rapid and continued increase. At the same time the mentality was markedly improved. Formerly she was phlegmatic, not easily aroused, did not play with other children, and was backward in

talking. She has greatly changed in appearance, manners, and desire to play and talk (Figs. 126, 127, 128, and 129).

In this case so little A-iodin was given that no toxic symptoms were produced and only a tonic effect resulted. The cretin is abnormal because of the absence of something. This deficiency can apparently be supplied by the administration of very small amounts ($\frac{1}{80}$ grain per day) of the A-iodin compound.



Fig. 130.—Patient with myxedema on entering hospital.

Another case similar to this one in respect to the effect on the mentality was observed with an adult suffering from myxedema. For six months this patient was treated with B alone. At the end of that time, although entirely relieved of subjective symptoms, she was still greatly troubled with inability to keep awake. She would fall asleep in street-cars, while resting on a park bench, etc., and had great difficulty in remaining awake even a few hours a day. When in this condition, small daily doses of A produced immediate

and striking relief. Within a few days the patient's whole appearance changed, her naturally bright and witty personality was fully restored, and the desire for sleep was reduced to normal (Figs. 130 and 131).

DOES THE THYROID CONTAIN MORE THAN ONE PHYSIOLOGICALLY ACTIVE SUBSTANCE?—This question cannot be definitely answered at this time, but there is evidence that at least one other substance besides the compound containing A-iodin produces



Fig. 131.—Same patient after six weeks' treatment with A and B. Patient lost 25 pounds, was relieved of many subjective symptoms, and regained her naturally bright mentality.

physiologic effects under certain conditions. The acid-soluble group of constituents, designated B, produces no apparent effect when given to normal dog or man, but certain symptoms of myxedema and some conditions of the skin appear to be relieved by the administration of B alone. The symptoms in myxedema relieved by B alone are burning sensations of the skin, with smarting, itching areas, soreness of bones and joints, and cramps of the muscles. No stress is laid on the relief of these symptoms, but they are mentioned in the possibility of drawing attention to the condition

in other cases. They are present only in the more severe types of myxedema.

Also, a dry, scaly skin with absence of perspiration in cases not diagnosed myxedema is relieved by B alone. Engman¹⁶ has treated a number of such cases, and among them two patients suffering from dermatitis exfoliativa. In practically all cases improvement has been noted, and in no case have there been any toxic symptoms produced. At our clinic, 92 cases have been treated with B constituents, and in no case have there been any toxic effects noticed. Twelve cases of cretinism and mongols have been treated over thirty days with large doses of B. Pulse-rate, respiration, temperature, and weight were taken for the entire period. While there were individual variations, the average results showed no apparent toxic effects.

This non-toxic effect of the B group of constituents is in strong contrast with the A group, since they both contain iodine. The iodine-containing compound in A has been isolated, and its toxicity shown; the iodine in B is in organic combination, but the nucleus to which it is attached is unknown and no relation of iodine to activity is evident. We do know that the compound containing iodine in B is not the same substance as the compound containing iodine in A, and there is evidence that these compounds exist independently in the gland (Fig. 132).

Plummer¹⁷ gives the clinical aspects of excessive activity of the thyroid as follows:

"All of the associated facts make it seem highly probable that the syndrome accompanying hyperplastic thyroid is in the main directly attributable to excessive thyroid function. Assuming this to be true, we can in a general way point out the action of the product of this activity.

"The effect of small doses continued over a relatively short time is cerebral excitation, vasomotor dilatation, rise in blood-pressure, stimulation of the heart, and general metabolism. Moderate doses cause cerebral irritability, mental and muscular incoördination, free perspiration, loss of weight and strength, and cardiac insufficiency. Large doses exaggerate the preceding effects; mental depression follows cerebral irritability; vomiting and nausea result

from a dose but little short of fatal. Relatively small doses continued over a long period give rise to the evidence of more per-

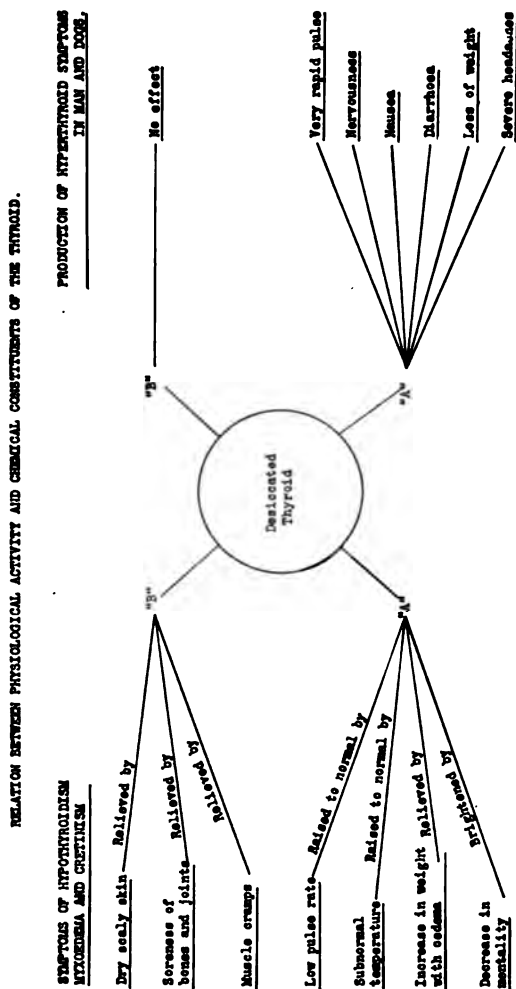


Fig. 132. — Relation between physiologic activity and chemical constituents of the thyroid.

manent types of damage, such as cardiac arrhythmia, cardiac fibrillation, hypertension, etc.

EFFECT ON DOGS OF ADMINISTERING A CONTAINING ABOUT
5 PER CENT. OF IODIN

TABLE I.—A-IODIN INJECTED SUBCUTANEOUSLY, 1 MGM. PER KILO
BODY WEIGHT

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
June 23, 1914....	116	38.9	11.12	..	All following injections subcutaneous.
June 24, 1914....	110	37.9	11.12	1
June 25, 1914....	110	38.0	11.12	1
June 26, 1914....	110	38.0	11.12	1
June 27, 1914....	102	37.8	10.91	1
June 28, 1914....	106	37.8	10.91	1
June 29, 1914....	106	37.9	10.45	1
June 30, 1914....	102	37.9	10.45	1
July 1, 1914....	102	37.9	10.59	1
July 2, 1914....	102	37.9	10.59	1
July 3, 1914....	106	37.8	10.59	1
July 4, 1914....	10.59	1
July 5, 1914....	108	37.9	10.68	1
July 6, 1914....	106	37.9	10.59	1
July 7, 1914....	10.59	1
July 8, 1914....	108	37.9	10.45	1
July 9, 1914....	110	38.5	10.22	$\frac{1}{2}$	10.4 mgm. A-iodin.
July 10, 1914....	142	38.8	10.22	1	10.4 mgm. A-iodin.
July 11, 1914....	136	38.8	10.00	1	10.4 mgm. A-iodin.
July 12, 1914....	136	39.0	10.00	1	10.4 mgm. A-iodin.
July 13, 1914....	220	39.2	10.15	1	10.4 mgm. A-iodin.
July 14, 1914....	250	38.8	10.00	1
July 15, 1914....	144	38.9	9.65	1
July 16, 1914....	126	38.9	9.85	1
July 17, 1914....	126	38.5	9.85	1
July 18, 1914....	110	38.4	10.00	$\frac{1}{2}$
July 19, 1914....	114	...	10.00	$\frac{1}{2}$
July 20, 1914....	130	38.9	10.00	$\frac{1}{2}$
July 21, 1914....	125	38.7	9.85	1
July 22, 1914....	118	38.7	10.15	1
July 23, 1914....	116	38.5	10.30	1
July 24, 1914....	116	37.8	10.28	1
July 25, 1914....	116	38.0	10.45	1
July 26, 1914....	1
July 27, 1914....	108	38.1	10.68	$\frac{3}{4}$
July 28, 1914....	100	38.3	10.45	$\frac{1}{2}$
July 29, 1914....	96	38.0	10.22	1
July 30, 1914....	96	37.9	10.22	1
July 31, 1914....	92	37.8	10.30	1
Aug. 1, 1914....	92	38.3	10.22	$\frac{3}{4}$

Diet, 200 grams dog biscuit per day.

Appetite judged on scale of 0 to 1 according to food eaten. The entire day's ration was offered to the dog but once every day; the portion not eaten within ten to fifteen minutes was removed.

EFFECT OF INJECTION OF A CONTAINING BUT LITTLE IODIN; OF
B-IODIN AND OF POTASSIUM IODIDTABLE II.—A, FROM SHEEP THYROID CONTAINING VERY LITTLE
IODIN

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
July 16, 1914....	100	38.7	10.00	0
July 17, 1914....	96	38.2	9.88	$\frac{1}{2}$
July 18, 1914....	126	38.1	9.68	$\frac{1}{2}$
July 19, 1914....	120
July 20, 1914....	118	38.2	10.00	$\frac{1}{2}$
July 21, 1914....	118	37.9	9.88	1	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 22, 1914....	102	38.3	10.10	1	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 23, 1914....	110	38.4	10.00	$\frac{3}{4}$	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 24, 1914....	106	38.4	10.00	1	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 25, 1914....	114	38.8	9.88	1	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 26, 1914....	132	1	400 mgm. of A from sheep thyroid containing 0.16 mgm.I.
July 27, 1914....	118	39.0	10.25	1
July 28, 1914....	110	39.2	10.10	1
July 29, 1914....	120	39.0	10.25	1
July 30, 1914....	120	38.3	10.30	1
July 31, 1914....	118	37.9	10.25	1
Aug. 1, 1914....	110	38.0	10.25	1

Diet, 200 grams of dog biscuit per day.

No apparent effect was produced after injection of A from sheep thyroids very low in iodine. The dog did not develop any other apparent symptoms, as nervousness or tremor.

TABLE III.—A, FROM COLLOID GOITERS CONTAINING VERY LITTLE IODIN

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
July 16, 1914....	132	38.5	5.91	$\frac{1}{2}$
July 17, 1914....	120	38.5	5.62	$\frac{1}{2}$
July 18, 1914....	120	39.5	5.91	1
July 19, 1914....	120
July 20, 1914....	120	39.3	6.02	1
July 21, 1914....	120	38.5	5.91	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 22, 1914....	120	38.9	6.12	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 23, 1914....	108	39.0	6.20	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 24, 1914....	106	38.4	5.80	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 25, 1914....	118	38.9	5.80	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 26, 1914....	120	1	200 mgm. A from colloid goiters, 0.5 mgm. iodine per day.
July 27, 1914....	118	39.0	6.12	1
July 28, 1914....	120	39.0	5.98	$\frac{1}{2}$
July 29, 1914....	102	38.8	6.02	$\frac{1}{2}$
July 30, 1914....	116	38.7	6.22	1
July 31, 1914....	104	38.9	6.28	1
Aug. 1, 1914....	104	38.7	6.22	1
Aug. 2, 1914....	104	5.98	1
Aug. 3, 1914....	104	6.12	1
Aug. 4, 1914....	104	6.22	1
Aug. 5, 1914....	104	6.22	1
Aug. 6, 1914....	106	6.28	1
Aug. 7, 1914....	118
Aug. 8, 1914....	108	1
Aug. 9, 1914....	1
Aug. 10, 1914....	102	6.22	1
Aug. 11, 1914....	106	1
Aug. 12, 1914....	102	5.98	1
Aug. 13, 1914....
Aug. 14, 1914....	100
Aug. 15, 1914....	106	6.02
Aug. 16, 1914....
Aug. 17, 1914....	100	6.02	1
Aug. 18, 1914....	106	6.08	1	12 mgm. A-iodine.
Aug. 19, 1914....	116	38.8	6.02	1	12 mgm. A-iodine.
Aug. 20, 1914....	150	38.8	5.98	$\frac{1}{2}$	12 mgm. A-iodine.
Aug. 21, 1914....	160	38.9	5.91	1	12 mgm. A-iodine.

Diet, 120 grams of dog biscuit per day.

Similar to Table VII, except A from colloid goiters low in iodine was used instead of A from sheep thyroid. A subsequent injection of 12 mgm. of A-iodine caused the typical increase in pulse-rate and other symptoms.

TABLE IV.—B-IODIN, 1 MGM. PER KILO BODY WEIGHT. LATER
A-IODIN, 1 MGM. PER KILO BODY WEIGHT

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
June 23, 1914....	106	38.4	7.28	0	All following injections given subcutaneously.
June 24, 1914....	110	38.6	7.28	1
June 25, 1914....	115	38.5	7.28	1
June 26, 1914....	126	39.5	7.45	1
June 27, 1914....	114	38.8	7.40	1
June 28, 1914....	116	38.9	7.40	1
June 29, 1914....	116	38.8	7.15	1	7.35 mgm. B-iodin.
June 30, 1914....	122	38.3	6.81	1	7.35 mgm. B-iodin.
July 1, 1914....	128	39.2	6.81	1	7.35 mgm. B-iodin.
July 2, 1914....	123	38.7	6.81	$\frac{1}{4}$	7.35 mgm. B-iodin.
July 3, 1914....	123	38.9	6.70	$\frac{1}{2}$	7.35 mgm. B-iodin.
July 4, 1914....	126	38.4	6.60	1	7.35 mgm. B-iodin.
July 5, 1914....	123	38.5	6.60	$\frac{1}{2}$	7.35 mgm. B-iodin.
July 6, 1914....	126	39.0	6.70	$\frac{1}{2}$	7.35 mgm. B-iodin.
July 7, 1914....	128	38.9	6.60	1	7.35 mgm. B-iodin.
July 8, 1914....	126	38.9	6.70	1	7.35 mgm. B-iodin.
July 8, 1914....	126	38.9	6.70	1	7.35 mgm. B-iodin.
July 9, 1914....	123	39.1	6.92	1
July 10, 1914....	123	38.8	6.85	1
July 11, 1914....	120	39.1	7.05	1
July 12, 1914....	126	39.1	7.05	1
July 13, 1914....	126	39.0	7.05	1
July 14, 1914....	110	39.0	6.92	$\frac{1}{4}$
July 15, 1914....	110	38.9	7.05	1
July 16, 1914....	110	38.8	7.05	1
July 17, 1914....	110	38.8	7.05	1
July 18, 1914....	110	38.9	6.92	1
July 19, 1914....	110
July 20, 1914....	118	39.2	7.15	1
July 21, 1914....	116	38.9	7.15	1
July 22, 1914....	120	38.9	7.15	1	7.35 mgm. A-iodin.
July 23, 1914....	132	38.4	7.28	1	7.35 mgm. A-iodin.
July 24, 1914....	140	38.4	7.28	1	7.35 mgm. A-iodin.
July 25, 1914....	146	39.1	6.81	1	7.35 mgm. A-iodin.
July 26, 1914....	156	6.81	1	7.35 mgm. A-iodin.
July 27, 1914....	186	39.4	7.15	$\frac{3}{4}$	7.35 mgm. A-iodin.
July 28, 1914....	160	39.5	6.81	$\frac{1}{4}$	7.35 mgm. A-iodin.
July 29, 1914....	164	39.6	6.92	1	7.35 mgm. A-iodin.
July 30, 1914....	150	38.9	6.81	1	7.35 mgm. A-iodin.
July 31, 1914....	152	38.9	6.81	1	7.35 mgm. A-iodin.
Aug. 1, 1914....	148	39.0	6.70	1
Aug. 2, 1914....	148	6.70	1
Aug. 3, 1914....	144	6.48	$\frac{3}{4}$
Aug. 4, 1914....	126	6.65	1
Aug. 5, 1914....	132	6.81	1
Aug. 6, 1914....	126	6.81	1
Aug. 7, 1914....	118	6.81	1
Aug. 8, 1914....	108	6.92	1
Aug. 9, 1914....	6.85	1
Aug. 10, 1914....	108	6.85	1

Diet, 128 grams dog biscuit daily.

Injection of B-iodin 1 mgm. per kilo did not cause any appreciable change in pulse-rate or produce nervous symptoms. A subsequent injection of A-iodin, using the same amount per kilo, produced the typical effects.

"Most of the variations in the course and severity of this clinical syndrome can be explained by an equation, taking into consideration the size of the dose, the length of its administration, the general and local susceptibility of the individual to the toxin. This conception in no way invalidates the possibility of an antitoxic action, relation of the thyroid to other ductless glands, more or less perversion of the thyroid secretions, etc."

At the present time there are no satisfactory means of recording, in a quantitative way, the degree of nervous irritability or the increased cerebral activity produced by administration of thyroid preparations. It is possible, therefore, to record only those changes which are expressed in terms of measurable quantities, the pulse-rate, weight, temperature, and nitrogen elimination, but changes in these factors are accompanied by many other effects which, to the observer, are as striking and as important. The tables contain the records of several experiments on animals and observations on patients, but the mere tabulation of pulse-rates cannot convey an adequate or comprehensive picture of the changes in any case. An increase in the pulse-rate of A. J. G. from 86 to 144 was accompanied by headaches, loss of appetite, and a distinct tremor, with dyspnea, but no quantitative record could show these other symptoms.

TABLE V.—IODIN IN FORM OF POTASSIUM IODID, 5 MGM. PER KILO

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
Sept. 9, 1914....	120	38.4	5.70	1
Sept. 10, 1914....	118	1	30 mgm. iodin as KI.
Sept. 11, 1914....	120	38.4	1	30 mgm. iodin as KI.
Sept. 12, 1914....	114	5.50	1	30 mgm. iodin as KI.
Sept. 13, 1914....	114	5.35	1	30 mgm. iodin as KI.
Sept. 14, 1914....	108	38.5	5.35	1	30 mgm. iodin as KI.
Sept. 15, 1914....	90	38.9	5.25	1	30 mgm. iodin as KI.
Sept. 16, 1914....	100	5.25	1	30 mgm. iodin as KI.
Sept. 17, 1914....	90	5.25

Injections of potassium iodid in amount six times as large as is necessary to produce toxic symptoms with A-iodin caused no apparent change.

TABLE VI.—EFFECT OF INJECTION OF THE COMPOUND IN A CONTAINING IODIN, PARTIALLY PURIFIED. IODIN CONTENT, 25 PER CENT.

DATE	PULSE	TEMPERATURE, CENTIGRADE	WEIGHT, KILOS	APPETITE	TREATMENT
Dec. 7, 1914....	107	38.9	8.64	0
Dec. 8, 1914....	107	38.8	8.64	$\frac{1}{2}$
Dec. 9, 1914....	107	38.8	8.64	$\frac{1}{2}$	25 mgm. A-iodin.
Dec. 10, 1914....	124	39.0	8.41	$\frac{1}{2}$	25 mgm. A-iodin.
Dec. 11, 1914....	160-80	39.2	8.30	$\frac{1}{2}$
Dec. 12, 1914....	142	39.3	8.30	$\frac{1}{2}$
Dec. 13, 1914....	150	39.3	8.18	$\frac{1}{2}$
Dec. 14, 1914....	154	39.1	8.18	$\frac{1}{2}$
Dec. 15, 1914....
Dec. 16, 1914....	135	39.1	8.18	$\frac{1}{2}$
Dec. 17, 1914....	120	38.9	8.18	$\frac{1}{2}$
Dec. 18, 1914....	110	39.1	8.18	$\frac{1}{2}$

Diet, 170 grams of dog biscuit per day.

Typical effects were produced by this A purified until its iodine content was 25 per cent.

EFFECT OF INJECTION OF THE COMPOUND IN A CONTAINING IODINE
PURIFIED TO A SINGLE CRYSTALLINE COMPOUND WITH A
CONSTANT IODINE CONTENT OF 60 PER CENT.

TABLE VII.—CRYSTALLINE COMPOUND CONTAINING 60 PER CENT OF IODINE, ISOLATED FROM A. WEIGHT OF DOG, 6.35 KILOS

DATE	PULSE	TREATMENT
January 11, 1915.....	110
January 12, 1915.....	110	20 mgm. A-iodine crystals.
January 13, 1915.....	130	20 mgm. A-iodine crystals.
January 14, 1915.....	160	20 mgm. A-iodine crystals.
January 15, 1915.....	167-176
January 16, 1915.....
January 17, 1915.....	196
January 18, 1915.....	195-210
January 19, 1915.....	156-176
January 20, 1915.....	134-162
January 21, 1915.....	150
January 22, 1915.....	134
January 23, 1915.....	140
January 24, 1915.....
January 25, 1915.....
January 26, 1915.....
January 27, 1915.....	150

The same typical effects on pulse-rate and nervous symptoms followed injection of the pure crystalline compound isolated from A.

The following tables show changes in the pulse-rate of patients after taking group A constituents in various stages of purity up to and including the crystalline form of the compound containing iodine:

**EFFECT OF ADMINISTERING GROUP A CONSTITUENTS CONTAINING
5 PER CENT. OF IODINE**

**TABLE VIII.—MRS. W. APPARENTLY NORMAL. WEIGHT, 103 KILOS.
AGED, FORTY-FIVE YEARS**

DATE	PULSE-RATE	AMOUNT OF A-IODINE PER DAY
November 13, 1914.....	86	Total amount, 152 mgm.
November 16, 1914.....	120	From November 13 to November 23, 5 mgm.
November 19, 1914.....	137
November 20, 1914.....	131
November 23, 1914.....	140	From November 23 to November 25, 4 mgm.
November 24, 1914.....	141
November 25, 1914.....	135	From November 25 to November 30, 8 mgm.
November 27, 1914.....	130
November 28, 1914.....	150
November 30, 1914.....	150	From November 30 to December 2, 9 mgm.
December 1, 1914.....	141
December 2, 1914.....	142	From December 2 to December 5, 12 mgm.
December 3, 1914.....	143
December 4, 1914.....	142

During this time, although the patient had rapid pulse, loss of appetite, and became nervous and dyspneic, the weight was but little affected.

**EFFECT OF ADMINISTERING GROUP A CONSTITUENTS CONTAINING
25 PER CENT. OF A-IODINE**

**TABLE IX.—A. J. G., MALE, NORMAL WEIGHT, 60 KILOS. AGED,
THIRTY-EIGHT YEARS**

DATE	PULSE-RATE	AMOUNT OF A-IODINE PER DAY
May 29, 1915.....	86	From May 29 to June 7, 3 mgm.
May 31, 1915.....	96
June 1, 1915.....	114
June 2, 1915.....	100
June 3, 1915.....	114
June 4, 1915.....	117
June 5, 1915.....	120
June 7, 1915.....	120	From June 7 to June 13, 6 mgm.
June 8, 1915.....	122	Total amount, 61 mgm.
June 9, 1915.....	125
June 10, 1915.....	130
June 11, 1915.....	130
June 12, 1915.....	138
June 13, 1915.....	144
June 14, 1915.....	144

EFFECT OF ADMINISTERING PURE CRYSTALLINE COMPOUND
ISOLATED FROM GROUP A CONSTITUENTS

TABLE X.—F. B., FEMALE, CRETIN, WEIGHT, 15 KILOS. AGED, SIX YEARS

DATE	PULSE-RATE	AMOUNT OF IODIN
March 5, 1915.....	124
March 6, 1915.....	106
March 8, 1915.....	117
March 9, 1915.....	117
March 10, 1915.....	120
March 11, 1915.....	117	From March 11 to March 25, 0.5 mgm. of A-iodin per day.
March 12, 1915.....	120	
March 13, 1915.....	117	Total amount, 7 mgm. A-iodin.
March 14, 1915.....	120
March 15, 1915.....	123
March 16, 1915.....	123
March 17, 1915.....	126
March 18, 1915.....	120
March 19, 1915.....	126
March 20, 1915.....	128
March 22, 1915.....	140
March 23, 1915.....	133
March 24, 1915.....	142
March 25, 1915.....	142
March 26, 1915.....	140

This cretin had not previously been treated with thyroid.

SUMMARY

1. By an alkaline alcoholic hydrolysis the thyroid proteins are broken into many simpler constituents, which, by their solubility in acids, are separated into two groups. Those constituents insoluble in acid are designated group A, and those soluble, group B. No definite crystalline compound has been isolated from group B, but it appears to be composed of mixtures of amino-acid complexes. About one-half the total iodine in the thyroid proteins appears among the group B constituents. The nucleus to which the iodine is attached is unknown.

By continued hydrolysis the group A compounds have been further separated, and the iodine-containing compound has been isolated in pure crystalline form, having a constant iodine content of 60 per cent. Its exact formula cannot now be given, but its chemical properties are best expressed by di-iodo-indol-carboxylic acid.

2. Physiologic tests on dogs and human beings have shown that no toxic effects can be produced by any of the constituents of group

B. Group A constituents, however, produce the so-called hyperthyroid symptoms: increase in pulse-rate, with tachycardia, increase of nitrogen elimination, with loss of weight, and increase in nervous irritability, etc. Further investigation showed that the production of these symptoms was proportional to the iodine content, that partial purification of A did not destroy the activity, and finally that the compound containing A-iodine produced these effects in all stages of purity up to and including the pure crystalline form.

3. The amount of the A-iodine compound necessary to produce symptoms is extremely small. One-half milligram ($\frac{1}{120}$ of a grain) per day produced marked effects in a cretin weighing 15 kilos. The susceptibility of animals and man to this compound varies greatly, but the human being responds much quicker and to a far greater degree than the dog. Some form of tolerance for the compound is produced.

In very small doses the A-iodine compound exerts a tonic effect, and appears to be essential for normal growth and life.

4. Administration of A-iodine to man produces changes in the cardiogram.

5. Although B produces no toxic effects, it appears to possess some slight physiologic properties in cases of myxedema and certain conditions of the skin.

The toxic properties of A are due to the iodine-containing compound which has been isolated. There appears to be no relation between activity and iodine in B.

During the course of this investigation I have become indebted to Dr. F. C. Wood, director of the pathologic department, St. Luke's Hospital, New York City; to Dr. C. B. Cauldwell, of Lincoln, Illinois, and to Dr. M. F. Engman, of St. Louis, for clinical observations. In the Mayo Clinic, I wish to thank especially Dr. C. H. Mayo, Dr. H. S. Plummer, and Dr. L. B. Wilson for the opportunity to carry out the investigation and for encouragement, advice, and help during the work.

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THE RELATIONSHIP OF THE PATHOLOGIC HISTOLOGY AND THE IODIN COMPOUNDS OF THE HUMAN THYROID *

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The present study presents some new evidence in the solution of the problems of the relationships between the clinical, pathologic, and chemical findings in cases of human goiter. The scope of the study is limited to 566 cases, from which specimens have been analyzed chemically in the course of a general investigation of the iodine compounds of the thyroid. The cases were not selected, but were taken at random in the order as operated on from the patients under treatment in the Mayo Clinic during 1914.

CLINICAL CLASSIFICATION.—The clinical classification of the cases into—(1) Hyperplastic toxic (“exophthalmic” goiter); (2) non-hyperplastic toxic with high blood-pressure; (3) non-hyperplastic toxic with low blood-pressure; (4) non-hyperplastic questionably toxic with low blood-pressure, and (5) non-hyperplastic atoxic with low blood-pressure has been made by Plummer,^{1, 2} and follows his previous grouping. Though the terms “hyperplastic” and “non-hyperplastic” refer to the morphology of the gland, which cannot be shown until its removal, yet they have been used in making the clinical diagnoses by Plummer and his associates with but a negligible margin of error, as shown by the subsequent pathologic examination.

PATHOLOGIC CLASSIFICATION.—The pathologic classification is, with slight modification, that previously published by Wilson.³⁻¹⁰ The main divisions—(1) Primary hypertrophy and hyperplasia of

* Read before the Association of American Physicians, Washington, May 10, 1915. Reprinted from *Amer. Jour. Med. Sci.*, 1916, cli, 79-91. Copyright, 1916, by Lea and Febiger.

epithelium; (2) primary retention of colloid with atrophy of epithelium; (3) encapsulated adenomas, and (4) carcinomas, with their several subdivisions, are self-explanatory. As our study of the morphology of the thyroid in goiter has progressed, it has been found desirable to subdivide the group of regressing hyperplasias into subgroups—early, advanced, and very advanced regression. Also the undegenerated encapsulated adenomas, with colloid-filled acini, Group G, are so few in proportion to the degenerated adenomas, Group F, that in the present study the three subgroups have not been separated. The encapsulated adenomas have been separated from adenomatoses, and the latter included in the group described as primary retention of colloid with atrophy of epithelium.

CHEMICAL INVESTIGATION.—The methods employed in the determination of iodine and the dry weight of thyroid substance removed at operation were as follows:

The fresh gland was placed in a crystallizing dish, covered with a glass plate, and heated three or four hours in an oven at 100° C. This preliminary treatment removed a large portion of the water and made the gland cut more easily into smaller pieces. After the gland was cut into small pieces it was completely dried in a vacuum desiccator, and then ground to a fine powder in a coffee-mill, thoroughly mixed, and the iodine content determined¹¹ in a one-half gram portion. Two modifications of this procedure were employed for some of the glands. Instead of taking the entire fresh gland for purposes of desiccation, a known portion of the total was taken, and from the dried weight of this portion the dried weight of the total gland and the amount of iodine were calculated. The other modification consisted in taking a portion of the gland after it had been fixed in 4 per cent. formaldehyd. From this known portion the dried weight of the total gland was determined, and the total iodine based on this weight. Analysis of the formaldehyd solution showed that in every case an appreciable amount of iodine from the gland had passed into the formaldehyd solution. It was therefore necessary to determine the amount of iodine in this solution to obtain the total iodine originally present in the portion of the gland

removed at operation. The results obtained by these procedures were kept separate until after they were compared with the pathologic grouping. This comparison showed no appreciable differences between the three methods, so that in the final tabulation of results there was no discrimination made as to which method was employed for determining the total dried weight and the total iodine.

In addition to the determination of the total iodine, the dried thyroid substance of 58 thyroids was hydrolyzed by a method already published.¹³ This hydrolysis splits the proteins into simpler products and divides the total iodine into two chemically different groups. The α -iodine compound is insoluble in acids. The β -iodine compound is soluble. Both α - and β -iodine are in organic combinations, and there is evidence that β -iodine is not a decomposition product of the α -iodine compound, but that the two forms exist independently in the gland. Physiologic tests¹⁴ have shown that the α -iodine compound produces the typical effects of desiccated thyroid, but that the β -iodine compound has no toxic action. It therefore seemed desirable to determine the amount of α -, or toxic, iodine compound in some of the glands removed. For the determination of the amount of α -iodine in a given gland, the dry powdered gland was boiled in 90 per cent. alcohol in the presence of 1 per cent. sodium hydroxide for forty-eight hours, 2.5 grams of the dried thyroid per 100 c.c. of alcohol. At the end of the boiling, carbon dioxide was passed through the solution and the alcohol evaporated. The solution was then acidified with 20 per cent. sulphuric acid. The precipitate (α -constituents) was filtered and washed with a small amount of water. This precipitate was dissolved in sodium hydroxide. The amounts of iodine in the filtrate (β -constituents) and in the solution of the α -constituents were determined. This gave the amounts of α - and β -iodine, and the sum of these two the total iodine in the gland.

In connection with the determination of iodine, it may be said that the results obtained during the course of this investigation approximate 4000 determinations of iodine. From a comparison of duplicates and an inspection of the accuracy of the total series, it would appear that for this work the method used is entirely

adequate. The great advantage of obtaining a perfect "blank" where no iodine exists, of having no blue color flashed back from the starch iodine reaction after titration is finished, and the wide range in the amounts of iodine which come within the method, together with the shortness of time and inexpensive chemicals, have made this method the one of choice in our laboratory.

PROTOCOLS.—The bulk of the material makes publication of protocols obviously cumbersome. However, the protocols of the chemical analyses and pathologic examinations, with the microscopic sections, gross specimens, and the clinical histories are on file in the Mayo Clinic, and are open to study to any one interested. The results have been accurately compiled and condensed into a series of tables herewith presented.

DISCUSSION OF TABLES.—*Table I.*—The distribution of the cases into the several clinical and pathologic groups is given in totals, rather than in averages, that the numbers may serve as a basis for determining the percentage values in subsequent comparisons. It will be observed that the number of cases in certain groups (*A*, hyperplastic toxic; *D*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *H + F*, non-hyperplastic toxic and non-hyperplastic questionably toxic; *F*, questionably toxic; and the carcinomas) are so small as to make the averages of relatively little value. However, it would have been more inaccurate to omit these cases entirely, and attention will be called to the insufficient evidence presented in these groups, as the several comparative tables are discussed later. It should be noted that of the 425 cases of non-hyperplastic goiter, 197 presented symptoms which might have caused many of them to be diagnosed as "exophthalmic goiters" by clinicians elsewhere. Without analyzing in detail the distribution of these cases, it may be pointed out that the general distribution closely approximates that shown in a similar group of patients operated on in 1911 and 1912.⁹

Table II.—Table II shows the average age of the patients at the time their thyroids were removed. While the average age of the patients with hyperplastic toxic goiter is thirty-five years, it will be noted that the average age of those with early hypertrophy is only

GOITERS, CORRELATION OF PATHOLOGIC, CLINICAL, AND CHEMICAL DATA

TABLE I.—NUMBER OF CASES

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ('exophthalmic' goiter)	2. Non-hyperplastic toxic with high blood-pressure ('simple' goiter)	3. Non-hyperplastic toxic with low blood-pressure ('simple' goiter)	4. Non-hyperplastic toxic (?) with low blood-pressure ('simple' goiter)	5. Non-hyperplastic atoxic with low blood-pressure ('simple' goiter)	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	2					2
B. Advanced hyperplasia.....	44					44
C 1. Early regression of hyperplasia.....	98					98
C 2. Advanced regression of hyperplasia.....	96					96
C 3. Very advanced regression of hyperplasia.....	17					17
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	4	16	5	4	25	54
H. Diffuse atrophy of epithelium H+F. Diffuse atrophy of epithelium with included adenomas:		65	35	11	96	207
3. ENCAPSULATED ADENOMAS:						
E, F, G.....		27	9	2	47	85
4. CARCINOMAS.....		25	12	7	35	79
		3			1	4
Totals (Average).....	141	136	61	24	204	566

TABLE II.—AVERAGE AGES (IN YEARS)

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ('exophthalmic' goiter)	2. Non-hyperplastic toxic with high blood-pressure ('simple' goiter)	3. Non-hyperplastic toxic with low blood-pressure ('simple' goiter)	4. Non-hyperplastic toxic (?) with low blood-pressure ('simple' goiter)	5. Non-hyperplastic atoxic with low blood-pressure ('simple' goiter)	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	19					19
B. Advanced hyperplasia.....	34					34
C 1. Early regression of hyperplasia.....	98					98
C 2. Advanced regression of hyperplasia.....	95					95
C 3. Very advanced regression of hyperplasia.....	34					34
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	29	45	40	33	32	32
H. Diffuse atrophy of epithelium H+F. Diffuse atrophy of epithelium with included adenomas:		50	37	35	35	40
3. ENCAPSULATED ADENOMAS:						
E, F, G.....		49	33	38	36	40
4. CARCINOMAS.....		46	40	44	36	40
		44			42	44
Totals (Average).....	33	49	38	38	35	39

GOITERS, CORRELATION OF PATHOLOGIC, CLINICAL, AND CHEMICAL DATA

TABLE III.—AVERAGE DURATION OF GOITERS AND AVERAGE DURATION OF TOXIC SYMPTOMS (IN MONTHS)

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ("exophthalmic" roller)	2. Non-hyperplastic toxic with high blood-pressure ("simple" roller)	3. Non-hyperplastic toxic with low blood-pressure ("simple" roller)	4. Non-hyperplastic toxic (?) with low blood-pressure ("simple" roller)	5. Non-hyperplastic atoxic with low blood-pressure ("simple" roller)	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	9 (9)	9 (9)
B. Advanced hyperplasia.....	17 (10)	17 (10)
C 1. Early regression of hyperplasia.....	32 (18)	32 (18)
C 2. Advanced regression of hyperplasia.....	53 (35)	53 (35)
C 3. Very advanced regression of hyperplasia.....	68 (47)	68 (47)
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	132 (11)	216	276	204	156	209
H. Diffuse atrophy of epithelium.....	..	240	180	240	168	204
H + F. Diffuse atrophy of epithelium with included adenomas.....	..	216	156	240	168	180
3. ENCAPSULATED ADENOMAS:						
E, F, G.....	..	180	180	192	156	168
4. CARCINOMAS.....	..	192	300	252
Totals (averages).....	41	228	180	216	168	

TABLE IV.—AVERAGE SYSTOLIC BLOOD-PRESSURE

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ("exophthalmic" roller)	2. Non-hyperplastic toxic with high blood-pressure ("simple" roller)	3. Non-hyperplastic toxic with low blood-pressure ("simple" roller)	4. Non-hyperplastic toxic (?) with low blood-pressure ("simple" roller)	5. Non-hyperplastic atoxic with low blood-pressure ("simple" roller)	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	140	140
B. Advanced hyperplasia.....	138	138
C 1. Early regression of hyperplasia.....	147	147
C 2. Advanced regression of hyperplasia.....	132	132
C 3. Very advanced regression of hyperplasia.....	144	144
2. PRIMARY RETENTION OF COLLOID; ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	148	164	129	120	125	140
H. Diffuse atrophy of epithelium.....	..	171	130	128	120	141
H + F. Diffuse atrophy of epithelium with included adenomas.....	..	176	121	132	124	143
3. ENCAPSULATED ADENOMAS:						
E, F, G.....	..	171	129	126	128	144
4. CARCINOMAS.....	..	157	120	142
Totals (averages).....	143	171	128	127	123	

nineteen years, of those with advanced hyperplasia thirty-four years, and of those whose thyroids showed regression in the hyperplastic process it is thirty-eight, thirty-five, and thirty-four years respectively, in inverse order to the amount of regression. At first thought it would appear that this inversion of the average ages in relation to the amount of regression of hyperplasia is contradictory, but when the average ages are examined in the light of Table III, in which is shown the average duration of goiter in months, it will be seen that while the younger patients showed the greatest amount of epithelial regression, the duration of the goiter as well as the duration of symptoms were both also inversely as to age and directly as to the amount of regression. The same holds good in the four cases of clinically hyperplastic toxic goiter with secondary regeneration of the thyroid epithelium. Here the average age was twenty-nine years, and though the average duration of goiter was one hundred and thirty-two months, the average duration of symptoms was only eleven months. In this pathologic group (epithelial regenerations) the age-distribution of the patients in the various clinical classes is interesting, being twenty-nine years in the hyperplastic toxic, forty-five years in the non-hyperplastic toxic with high blood-pressure, fifty years in the non-hyperplastic toxics with low blood-pressure, thirty-three years in the non-hyperplastic questionably toxic, and thirty-two years in the non-hyperplastic atoxic cases.

The somewhat erratic age distribution of the cases in which the glands showed encapsulated adenomas, either alone (*E*, *F*, *G*) or included in diffuse colloid goiters (*H* + *F*), may not be wholly accidental, but may be due to the influence of the neoplasms. This point, however, is still under investigation in a larger series of cases.

Table III.—The average duration of goiters in months for the entire series, and the duration of hyperthyroidism in months for the hyperplastic series, is shown in Table III. The duration of the symptoms in the toxic non-hyperplastic cases is so difficult to determine with any degree of accuracy from the patient's description that no attempt has been made to state it in months. The difference between the period of duration of goiter in hyperplastic toxics, averaging forty-one months, and the period of duration of goiter in

the non-hyperplastic groups (the lowest of which is 156 months, and the highest 276 months, with an average of 192 months), is very marked, and constitutes a point in clinical diagnosis.

The maximum severity of symptoms, and the severity at the time of examinations in the several groups of hyperplastic toxic cases, indicated on a scale of 1, 2, 3, 4, and 5, averaged as follows:

	MAXIMUM SEVERITY	AT TIME OF EXAMINATION
A Early hypertrophy.....	1.0	1.0
B Advanced hyperplasia.....	2.6	2.5
C 1. Early regression.....	3.2	2.4
C 2. Advanced regression.....	3.6	2.5
C 3. Very advanced regression.....	3.4	2.0

Table IV.—The discussion of the systolic blood-pressure as presented in Table IV will be covered *in extenso* by Plummer.¹⁶ It is included in the present paper only for reference in relation to the percentage of iodine and total amount of iodine in the portion of removed gland. (See Tables VI and VII.)

Table V.—The average weight of the portion of the gland removed at operation in the hyperplastic toxic group was 57 grams, as compared with 55 grams, the average weight of the removed portion in the 1911 and 1912 cases.⁹ The average weight of the removed portion of the 425 cases of non-hyperplastic thyroids was 168 grams, as compared with 171 grams, the average weight of the non-hyperplastics in the 1911 and 1912 cases.⁹ This is of significance in showing the great disparity in size between the thyroids from hyperplastic toxic and those from non-hyperplastic toxic cases as previously noted.^{3,9} In the individual groups the removed portion of gland is larger in the cases of high blood-pressure than in the several pathologic groups with low blood-pressure.

Table VI.—The variation in the percentage of iodine in the dried gland in the several histologic types of thyroids from hyperplastic toxic cases is most marked. Starting in with the cases of early hypertrophy, the percentage is 0.11. It drops thence to 0.03 in the advanced hyperplasias, rises to 0.07 in the early regressions, to 0.16 in the advanced regressions, and to 0.19 in the very advanced regressions. A comparison of these percentages with those showing

GOITERS, CORRELATION OF PATHOLOGIC, CLINICAL, AND CHEMICAL DATA

TABLE V.—AVERAGE WEIGHT OF REMOVED GLAND (FRESH) IN GRAMS

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ("exophthalmic goiter")	2. Non-hyperplastic toxic with high blood-pressure ("simple goiter")	3. Non-hyperplastic toxic with low blood-pressure ("simple goiter")	4. Non-hyperplastic toxic (?) with low blood-pressure ("simple goiter")	5. Non-hyperplastic atoxic with low blood-pressure ("simple goiter")	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	46					46
B. Advanced hyperplasia.....	59					59
C 1. Early regression of hyperplasia.....	56					56
C 2. Advanced regression of hyperplasia.....	53					53
C 3. Very advanced regression of hyperplasia.....	70					70
2. PRIMARY RETENTION OF COLLOID ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	42	175	146	151	171	159
H. Diffuse atrophy of epithelium.....		223	169	170	158	181
H + F. Diffuse atrophy of epithelium with included adenomas.....		189	112	206	183	179
3. ENCAPSULATED ADENOMAS:						
E, F, G.....		109	125	140	108	114
4. CARCINOMAS.....		730			140	583
Totals (averages).....	57	190	150	107	157	137

TABLE VI.—AVERAGE PER CENT. OF IODIN IN DRIED THYROID

PATHOLOGIC CLASSIFICATION	CLINICAL CLASSIFICATION					
	1. Hyperplastic toxic ("exophthalmic goiter")	2. Non-hyperplastic toxic with high blood-pressure ("simple goiter")	3. Non-hyperplastic toxic with low blood-pressure ("simple goiter")	4. Non-hyperplastic toxic (?) with low blood-pressure ("simple goiter")	5. Non-hyperplastic atoxic with low blood-pressure ("simple goiter")	Totals (averages)
1. PRIMARY HYPERTROPHY AND HYPERPLASIA OF EPITHELIUM:						
A. Early hypertrophy and hyperplasia.....	0.11					0.11
B. Advanced hyperplasia.....	0.03					0.03
C 1. Early regression of hyperplasia.....	0.07					0.07
C 2. Advanced regression of hyperplasia.....	0.16					0.16
C 3. Very advanced regression of hyperplasia.....	0.19					0.19
2. PRIMARY RETENTION OF COLLOID ATROPHY OF EPITHELIUM:						
D. Secondary regeneration of epithelium.....	0.07	0.08	0.14	0.05	0.05	0.07
H. Diffuse atrophy of epithelium.....		0.08	0.11	0.08	0.08	0.08+
H + F. Diffuse atrophy of epithelium with included adenomas.....		0.09	0.12	0.05	0.06	0.07
3. ENCAPSULATED ADENOMAS:						
E, F, G.....		0.07	0.02	0.04	0.06	0.06
4. CARCINOMAS.....		0.003			0.07	0.02
Totals (averages).....	0.10	0.08	0.10	0.06	0.06+	0.085

percentages of iodine in the various non-hyperplastic thyroids shows that in no subgroup of the latter division does the percentage of iodine rise as high as that in the thyroids from cases with advanced regression in hyperplastic glands.

In the pathologic groups of the non-hyperplastic series the secondary regenerations (type D) present both the highest and the lowest percentages aside from certain low averages in the encapsulated adenomas and the carcinomas. The diffuse epithelial atrophies (type H) vary the least. The encapsulated adenomas, while generally low, vary from 0.02 to 0.07.

In the individual clinical groups it is interesting to note that in all, except the adenomas, the percentage of iodine is highest (average, 0.1 per cent.) in the non-hyperplastic toxic cases with low blood-pressure. The next in amount are the cases of non-hyperplastic toxic with high blood-pressure (average, 0.08 per cent.). In general, the percentage is lowest in the non-hyperplastic atoxic (average, 0.06 per cent.). Attention is called to this inversion of the order of the percentage amounts in relation to clinical symptoms over those observed in the cases of hyperplastic goiter.

A tabulation of both groups of non-hyperplastic toxic cases in comparison with the non-hyperplastic atoxic cases shows that in 84 per cent. of the atoxic the percentage of iodine was under 0.1, while but 68 per cent. of the toxic cases were under 0.1.

Table VII.—In the hyperplastic toxic cases the total amount of iodine in the portion of the gland removed follows the percentage of iodine, since the portion of gland removed in these cases is fairly equal in the several groups. The amount averages 9.2 mgm. in early hypertrophy, drops to 3.4 mgm. in the advanced hyperplasias, rises to 8 mgm. in the early regressions, to 14.2 mgm. in the advanced regressions, and to 21.9 mgm. in the very advanced regressions. The total amount in the cases with secondary regeneration of epithelium, which showed symptoms placing them in the hyperplastic toxic clinical group, is the smallest of any of the groups except the advanced hyperplastic toxics and carcinomas.

In the non-hyperplastics, the largest amount is in the toxics with low blood-pressure (23.8 mgm.), while in the atoxics the

CASES, CORRELATION OF PATHOLOGIC, CLINICAL AND CHEMICAL DATA

TABLE VIII.—AVERAGE PERCENTAGE OF c-MOSIN
of DETECTIVALS shown in parentheses

Primary Classification		Clinical Classification					Clinical Classification						
		1. Hyperplastic toxic ("exophthalmic" goiter)	2. Non-hyperplastic toxic with high blood-pressure ("simple" goiter)	3. Non-hyperplastic toxic with low blood-pressure ("simple" goiter)	Totals (averages)	1. Hyperplastic toxic ("exophthalmic" goiter)	2. Non-hyperplastic toxic with high blood-pressure ("simple" goiter)	3. Non-hyperplastic toxic with low blood-pressure ("simple" goiter)	Totals (averages)	1. Hyperplastic toxic ("exophthalmic" goiter)	2. Non-hyperplastic toxic with high blood-pressure ("simple" goiter)	3. Non-hyperplastic toxic with low blood-pressure ("simple" goiter)	Totals (averages)
1	Primary Hyperthyroidism and Hyperemia in Kretschmann's	0 2	14 2	25 0	14 9	7 (1) 16(11)	14 2	25 0	14 9	7 (1) 16(11)	14 2	25 0	14 9
2	A Early hyperthyroidism and hyperplasia	5 4	14 2	25 0	23 9	16(11)	14 2	25 0	23 9	16(11)	14 2	25 0	23 9
3	B Advanced hyperthyroidism	8 0	14 2	25 0	18 0	31 (8)	14 2	25 0	18 0	31 (8)	14 2	25 0	18 0
4	C 1 Early regression of hyperplasia	14 2	14 2	25 0	10 0	31 (6)	14 2	25 0	10 0	31 (6)	14 2	25 0	10 0
5	C 2 Advanced regression of hyperplasia	21 0	14 2	25 0	4 4	37 (4)	21 0	25 0	4 4	37 (4)	21 0	25 0	4 4
6	D Secondary regeneration of epithelium	5 7	10 0	25 0	12 1	16 (1)	10 0	25 0	12 1	16 (1)	10 0	25 0	12 1
7	H Diffuse atrophy of epithelium	25 0	25 0	25 0	18 4	33 (4)	25 0	25 0	18 4	33 (4)	25 0	25 0	18 4
8	I 1 F Diffuse atrophy of epithelium with included adenoma	27 5	27 5	25 0	11 1	25 (1)	27 5	25 0	11 1	25 (1)	27 5	25 0	11 1
9	I 2 F, a and b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z, aa, ab, ac, ad, ae, af, ag, ah, ai, aj, ak, al, am, an, ao, ap, aq, ar, as, at, au, av, aw, ax, ay, az, ba, bb, bc, bd, be, bf, bg, bh, bi, bj, bk, bl, bm, bn, bo, bp, bq, br, bs, bt, bu, bv, bw, bx, by, bz, ca, cb, cc, cd, ce, cf, cg, ch, ci, cj, ck, cl, cm, cn, co, cp, cq, cr, cs, ct, cu, cv, cw, cx, cy, cz, da, db, dc, dd, de, df, dg, dh, di, dj, dk, dl, dm, dn, do, dp, dq, dr, ds, dt, du, dv, dw, dx, dy, dz, ea, eb, ec, ed, ee, ef, eg, eh, ei, ej, ek, el, em, en, eo, ep, eq, er, es, et, eu, ev, ew, ex, ey, ez, fa, fb, fc, fd, fe, ff, fg, fh, fi, fj, fk, fl, fm, fn, fo, fp, fq, fr, fs, ft, fu, fv, fw, fx, fy, fz, ga, gb, gc, gd, ge, gf, gg, gh, gi, gj, gk, gl, gm, gn, go, gp, gq, gr, gs, gt, gu, gv, gw, gx, gy, gz, ha, hb, hc, hd, he, hf, hg, hh, hi, hj, hk, hl, hm, hn, ho, hp, hq, hr, hs, ht, hu, hv, hw, hx, hy, hz, ia, ib, ic, id, ie, if, ig, ih, ii, ij, ik, il, im, in, io, ip, iq, ir, is, it, iu, iv, iw, ix, iy, iz, ja, jb, jc, jd, je, jf, jg, jh, ji, jj, jk, jl, jm, jn, jo, jp, jq, jr, js, jt, ju, jv, jw, jx, jy, jz, ka, kb, kc, kd, ke, kf, kg, kh, ki, kj, kk, kl, km, kn, ko, kp, kq, kr, ks, kt, ku, kv, kw, kx, ky, kz, la, lb, lc, ld, le, lf, lg, lh, li, lj, lk, ll, lm, ln, lo, lp, lq, lr, ls, lt, lu, lv, lw, lx, ly, lz, ma, mb, mc, md, me, mf, mg, mh, mi, mj, mk, ml, mm, mn, mo, mp, mq, mr, ms, mt, mu, mv, mw, mx, my, mz, na, nb, nc, nd, ne, nf, ng, nh, ni, nj, nk, nl, nm, nn, no, np, nq, nr, ns, nt, nu, nv, nw, nx, ny, nz, oa, ob, oc, od, oe, of, og, oh, oi, oj, ok, ol, om, on, oo, op, oq, or, os, ot, ou, ov, ow, ox, oy, oz, pa, pb, pc, pd, pe, pf, pg, ph, pi, pj, pk, pl, pm, pn, po, pp, pq, pr, ps, pt, pu, pv, pw, px, py, pz, qa, qb, qc, qd, qe, qf, qg, qh, qi, qj, qk, ql, qm, qn, qo, qp, qq, qr, qs, qt, qu, qv, qw, qx, qy, qz, ra, rb, rc, rd, re, rf, rg, rh, ri, rj, rk, rl, rm, rn, ro, rp, rq, rr, rs, rt, ru, rv, rw, rx, ry, rz, sa, sb, sc, sd, se, sf, sg, sh, si, sj, sk, sl, sm, sn, so, sp, sq, sr, ss, st, su, sv, sw, sx, sy, sz, ta, tb, tc, td, te, tf, tg, th, ti, tj, tk, tl, tm, tn, to, tp, tq, tr, ts, tt, tu, tv, tw, tx, ty, tz, ua, ub, uc, ud, ue, uf, ug, uh, ui, uj, uk, ul, um, un, uo, up, uq, ur, us, ut, uu, uv, uw, ux, uy, uz, va, vb, vc, vd, ve, vf, vg, vh, vi, vj, vk, vl, vm, vn, vo, vp, vq, vr, vs, vt, vu, vv, vw, vx, vy, vz, wa, wb, wc, wd, we, wf, wg, wh, wi, wj, wk, wl, wm, wn, wo, wp, wq, wr, ws, wt, wu, wv, ww, wx, wy, wz, xa, xb, xc, xd, xe, xf, xg, xh, xi, xj, xk, xl, xm, xn, xo, xp, xq, xr, xs, xt, xu, xv, xw, xx, xy, xz, ya, yb, yc, yd, ye, yf, yg, yh, yi, yj, yk, yl, ym, yn, yo, yp, yq, yr, ys, yt, yu, yv, yw, yx, yy, yz, za, zb, zc, zd, ze, zf, zg, zh, zi, zj, zk, zl, zm, zn, zo, zp, zq, zr, zs, zt, zu, zv, zw, zx, zy, zz	25 (30)	30 (3)	24 (8)	38 (1)	34 (16)	58						

amount averages 15 mgm. It should be noted that, though the amount of iodine in the portions of glands removed in the non-hyperplastic cases is greater than the amount removed in the hyperplastic cases, the comparison of the relative amounts in the total gland is not made on the same basis, since in the non-hyperplastics a very much larger proportion of the gland is removed at operation (frequently as much as $\frac{9}{10}$) than is removed at operation in hyperplastic cases (rarely more than $\frac{2}{3}$).

Thus, it is probable that the total amount of iodine in the entire gland in the cases of hyperplastic goiter with very advanced regression averages more than the total amount of iodine in the entire gland in the non-hyperplastic cases.

The averages of the total iodine of patients grouped as to age by half-decades shows no order or regularity, but a similar grouping of the average total amounts of iodine arranged by duration of goiter in half-decades results as is shown in the table on p. 432 and also in the table below.

ADDENDUM TO TABLE VII.—TOTAL IODINE AND DURATION OF GOITER

DURATION OF GOITER IN HALF-DECADES	NON-HYPERPLASTIC TOXIC		NON-HYPERPLASTIC ATOXIC	
	NUMBER OF CASES	AVERAGE TOTAL IODINE, MGm.	NUMBER OF CASES	AVERAGE TOTAL IODINE, MGm.
5—	30	19.6	23	13.7
5+	21	18.4	37	12.3
10+	26	21.3	28	16.9
15+	23	32.9	30	16.9
20+	22	28.3	20	22.5
25+	19	22.3	11	14.0
30+	12	22.1	1	13.5
35+	8	28.3	2	16.2
40+	11	28.3	3	16.0

While there are considerable fluctuations in the total amount of iodine present at the different half-decades, the most constant relationship is that at each half-decade the total amount in the toxic cases is materially more than is the total amount in the atoxic cases.

Table VIII.—The determination of the α -iodine has been made in too few cases to make the average percentages of much compara-

tive value, there being but 30 cases in the hyperplastic group and 28 in the non-hyperplastic group. It may, however, be noted that, in those groups in which a sufficient number of cases exist for comparison, the following order is presented:

In the cases of advanced hyperplasia, the percentage of the total iodine in the α form is 16 (11 cases), and rises to 35 (18 cases) in the advanced regressions. In the non-hyperplastic cases, if the two groups with toxic symptoms are placed together (11 cases), the average percentage of the total iodine in the α form is 30, while in the atoxic group (16 cases) the average percentage is 34. Thus it will be seen that there is a parallel relationship in the two groups, though until further data are obtained no great significance can be attached to it.

GENERAL DISCUSSION

1. The data herein presented furnish additional proof of the statements previously made by one of us,³ that the symptom complex, which is generally recognized as "typical Graves' disease," "exophthalmic goiter," etc., and sharply denoted by Plummer as hyperplastic toxic goiter, is constantly parallel in all its stages of development and regression with similar stages of development and regression in the parenchyma of the thyroid. This parallelism is shown in the average duration of goiter, the average duration of toxic symptoms, and in the progressive and regressive histologic changes.

Now, for the first time in detail the percentages and total amounts of iodine, the pathologic groups, and the clinical types have been compared in the same series of cases. As previously suggested by the work of Smith and Broders,¹⁵ a close parallelism obtains throughout the data from the three sources.

From previous investigations there seemed to be little doubt that the clinical picture of exophthalmic goiter is produced, either directly or indirectly, by hyperactivity of the thyroid; but until some definite substance had been isolated from the normal thyroid and from the pathologic glands and shown to be toxic in its nature, no final conclusion could be arrived at. The isolation in pure form

of a compound containing 60 per cent. of iodine,^{12, 13, 14} and the proof that this substance is highly toxic in nature, emphasized the importance of an investigation concerning the amount and nature of the iodine-containing compounds of the thyroid. It has been shown that the iodine in the glands exists in two independent forms of combination, only one of which, the α form, is toxic. We must therefore enlarge our conception of the physiologic action of the iodine compounds to include the action of this one, the toxicity of which is vastly greater than that of any other hitherto described.

It is significant to find that this α -iodine compound is present in the actively hyperplastic glands of advanced hyperplastic toxic goiters in only $\frac{1}{50}$ to $\frac{1}{20}$ the amount in which it is present in normal thyroids. This must be interpreted not as a reduced production of the toxic substance, but as the result of its greatly increased diffusion from the gland into the blood-stream. There is no quantitative measure of the secretory activity of the thyroid, but its storage capacity for the toxic substance is obviously proportional to its iodine content. If further observations support the relatively few herein recorded, it would seem to be a fair assumption that the α -iodine compound is responsible for the toxic symptoms in hyperplastic toxic goiter. The constant direct relationship between the clinical symptoms and pathologic picture and the reservoir capacity of the thyroid in hyperplastic toxic goiter is strikingly shown in Tables VI, VII, and VIII. The failure on the part of other pathologists to recognize this constant association, we believe, has been due—(1) to failure by clinicians to distinguish sharply between hyperplastic toxic goiter (“typical acute exophthalmic,” “Graves’ disease,” etc.) and the several indeterminate groups of non-hyperplastic toxic goiter (“atypical chronic Graves’ disease,” “cardio-vascular goiter,” etc.), and (2) failure to recognize the fact long ago suggested,² that the chemical constituents found in the thyroid are only the complement of those which must have gone out of the gland to have caused symptoms.

2. The relationship of the pathology and chemistry of non-hyperplastic thyroids to the various clinical groups of toxic and atoxic non-hyperplastic goiter is still far from being cleared up.

This is due—(1) to the difficulty in accurately grouping these cases clinically, (2) to the difficulty in securing accurate information as to the onset and course of the chronic symptoms, and (3) to the difficulty in interpreting long past primary pathologic changes in the light of present pathologic and chemical findings, since most of these patients seek surgical aid many years after the beginning of the goiter, and probably also several years after the beginning of symptoms. That the relationship of the histologic changes in the thyroids designated as epithelial regenerations is parallel with the iodine content of the glands, and to some extent with the clinical history of the patients from whom the glands were removed, is shown in the several tables.

One fact running through all the tables is that the amount of iodine in the gland parallels the clinical grouping. In the actively hyperplastic glands (group B) it has been shown that the amounts of iodine and α -iodine are very low, but in cases where regression has occurred (group C), the amounts of iodine are high. In contrast to this it was found that the amount of iodine in the non-hyperplastic toxic glands is higher than in the non-hyperplastic atoxic glands.

The clinical picture, in its most severe type, of patients with non-hyperplastic toxic goiter, approaches in many respects the picture of patients with hyperplastic toxic goiter. Assuming the same toxic substance to be the cause for all thyroid intoxication, the factors involved to produce varying clinical pictures are the daily amount of absorption of the toxic substance, the length of time during which this intoxication occurs, and the personal resistance of the patient. At present we have no conclusive evidence explaining the higher iodine content of toxic non-hyperplastic glands than that of the actively toxic hyperplastic glands, but it seems probable that the diffusibility from the gland of the α -iodine compound may be an important factor in determining whether or not a goiter produces toxic symptoms.

Further rearrangements of the clinical groups of non-hyperplastic goiter are in progress by Plummer, and further studies of the pathology and chemistry of the thyroids from these cases are now being made by us and will be reported later.

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PATHOLOGIC CHANGES IN THE MUSCULAR AND NERVOUS SYSTEMS IN GOITER *

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CLINICAL CLASSIFICATION

Clinically, cases of goiter for a long time have been roughly grouped as exophthalmic and simple. Plummer, however, has shown that such a classification is very inadequate and does not properly represent the clinical conditions met with. Many of the cases which are commonly designated "exophthalmic" are radically different in their mode of onset, periods of progress, and general symptomatology from the cases which every one readily recognizes as exophthalmic goiter, or Basedow's disease. And, on the other hand, many of the cases of so-called "simple" goiter, on careful clinical analysis, are shown to be far from simple, exhibiting evidence of chronic changes in vital organs, which can be explained only on the hypothesis that for a long time small amounts of some well-marked poison have been acting on the tissues.

PATHOLOGIC RELATIONSHIPS OF THE THYROID

In 1908, in a study of a large series of thyroids removed at operation from cases of then so-called "exophthalmic goiter," I showed that there were two very distinct types of lesions present in the glands. In one group were thyroids in which there was abundant evidence of early, advanced, or regressing hyperplasia of the parenchyma associated severally with various stages of complete elimination, partial retention, and very marked retention of secretion. In the other group, no evidence of these three stages of hyperplasia

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and associated secretion phenomena could be found, but the process, on the other hand, appeared to be one (a) either of a diffuse enlargement of the thyroid from simple retention of secretion without overactivity of the parenchyma, followed by atrophy of the same, or (b) the same process with secondary regeneration of epithelium in new acini within the walls of old acini lined with atrophic epithelium, or (c) definitely encapsulated adenomas made up of acini of a more or less embryonic appearance.

In a similar study, made in 1909, on a large series of thyroids from so-called "simple goiter" cases, I showed that, with such exceptions only as might come within a reasonable margin of error, no hyperplastic glands were found, and that all the cases, on the contrary, exhibited one or the other of the pictures found in the second class from so-called "exophthalmic goiter" cases.

Plummer, in reviewing the clinical histories of the cases in which I had made pathologic studies of the thyroid, noted that there were certain very distinct clinical characteristics in those cases in which the thyroids exhibited evidence of present or recent hyperplasia from those cases in which no such hyperplasia existed. He was, therefore, led to designate the clinical groups of goiter, the clinical evidence for the existence of which he had previously observed, according to the pathologic condition present in the gland, as "hyperplastic toxic," "non-hyperplastic toxic," and "non-hyperplastic atoxic."

The first group, the hyperplastic toxic cases, every experienced clinician will readily recognize as containing the more typical cases of the old so-called "exophthalmic" goiter group. The third class, the non-hyperplastic atoxics, similarly experienced clinicians will readily recognize as containing the non-symptomatic cases of the old so-called "simple" goiter group. The second class, the non-hyperplastic toxic, is the one most difficult to recognize clinically, and the one on which the greatest diversity of opinion concerning the classification therein of individual cases will continue to exist among clinicians with relatively limited experience with goiter. Broadly speaking, as defined by Plummer, the characteristics of this class, as distinguished from hyperplastic toxic goiters, rest on—

(1) Its chronicity (an average developmental period of over fourteen years, as compared with one averaging nine months in hyperplastic toxic goiter); (2) the relative absence of acute toxic symptoms (diarrhea, tachycardia, etc.); (3) the absence of exophthalmos (which, however, may be absent also in hyperplastic toxic goiter), and (4) the slow development of symptoms of chronic cardiovascular changes. The limitations of this second clinical group, the non-hyperplastic toxic goiters, are still not absolutely complete nor definite. Plummer's studies, however, have gone so far that during the last three years in the Mayo Clinic the margin of error in diagnosis, as controlled by subsequent pathologic examination of specimens from the patients operated on, has been reduced below 3 per cent. That is, the pathologic examination of thyroids removed in cases which had been diagnosed clinically as hyperplastic toxic, and of those which had been diagnosed clinically as non-hyperplastic toxic, before operation, showed that the clinician had been able to foretell the presence or absence of the pathologic hyperplasia of the thyroid in 97 per cent. of the patients.

Since the histology of thyroids from non-hyperplastic toxic goiter cases and those from non-hyperplastic atoxic cases is, on the whole, indistinguishable, and also since there is no way as yet of accurately measuring, even after the removal of the gland, the total functional capacity of its parenchyma, it is obvious that there is as yet no means by pathologic observations of checking the accuracy of the clinical differentiation between non-hyperplastic toxic goiter and non-hyperplastic atoxic goiter. This problem is one that Plummer and I have had under investigation for some time, but we have not been able to report any material progress therein. It is doubtful, indeed, if any pathologic differentiation may ever be shown between the thyroids from chronic toxic cases and chronic atoxic cases, since the condition of the gland at the time of its removal is apt to be far different from its condition years previous, at which time it was responsible for slowly developing toxic symptoms. The problem is further complicated also by the not infrequent occurrence, in these cases, of encapsulated adenomas, the clinical and pathologic relationships of which are still undeter-

mined. From the clinical standpoint, the data are often incomplete and inaccurate, as given by patients in histories extending over a number of years. From the pathologic standpoint it is incomplete, largely from the fact that only a portion of the gland is removed at operation. However, as the clinician's experience broadens he becomes able to elicit more accurate information in the clinical histories, and parallel with this, the pathologist's list of cases which have come to autopsy and thus yield complete data is gradually increasing.

CHEMISTRY

One of the greatest forward steps recently taken in the solution of the problems of goiter has been that by Kendall, who had discovered and isolated in pure crystalline form the active principle of the thyroid. This substance, which is analogous in the thyroid to adrenalin in the adrenal, is a definite chemical compound containing 60 per cent. of iodine. It occurs in the thyroids of all animals tested, under both normal and pathologic conditions. It is associated in the thyroid with another iodine compound or compounds, the exact chemical relationships of which have not been determined, but which appeared to be physiologically relatively inert. The active principle, which, for the sake of brevity, Kendall designates as "Alpha" iodine, is physiologically a highly active substance, and in even relatively small amounts very toxic. We have been accustomed to theorizing, since Baumann's discovery of iodothyronin, on the activity of the thyroid simply in terms of its iodine content. However, great discrepancies between the known activity of dried thyroid and of inorganic iodine compounds of relatively much greater iodine content have been often noted. The explanation lies in Alpha iodine, the physiologic activities of which are to iodine about as the physiologic activities of mercuric chlorid are to mercury. The average normal individual can ingest daily several grains of almost any inorganic compound of iodine without perceptible physiologic reaction. On the other hand, the administration of $\frac{1}{8}$ grain daily of Alpha iodine to a 200-pound healthy athlete will produce, within a few days, some of the characteristic symptoms of acute exophthalmic goiter, such as nervousness and tachycardia.

Therapeutically, Alpha iodine in minute doses, $\frac{1}{180}$ grain, by mouth, stimulates the growth and mental activities of cretins and of patients with myxedema, just as do large doses of desiccated thyroid. Since it is a chemically pure substance, however, the dose may be much more accurately determined than that of desiccated thyroid, specimens of which vary greatly not only in their total iodine content, but also in the relative amount of Alpha iodine, which they contain.

Kendall and I have recently completed a comparative study of the iodine content and the pathologic histology of thyroids from some 500 cases of goiter. Without going into detail, I may say that in every respect this study bears out what I have previously shown, that in hyperplastic toxic goiter the histologic condition of the gland is an accurate index of the clinical condition of the patient when the essential fact is taken into account that it must be the secretion which is made in the gland and has gone out therefrom which is causing symptoms, rather than the complementary secretion which is stored up within the gland. Thus we found that in the thyroids showing early hypertrophy and hyperplasia, removed from patients with early hyperplastic toxic goiter, the relative amount of total iodine and of Alpha iodine is lower than normal, that in the thyroids with advanced hyperplasia from patients with well-advanced hyperplastic toxic goiter the amount of total iodine and of Alpha iodine within the gland is reduced to a very low point, and that in thyroids with regressing hyperplasia, and the associated storage of secretion, removed from patients with regressing hyperplastic toxic goiter, the total amount, both of iodine and of Alpha iodine, returns to the normal level, and in very advanced cases is on the average materially higher than normal. This latter observation suggests that the process of elaboration of the iodine compound within the gland has gone on in excess even after the mechanism for its delivery into the circulation has been so modified as to cause again its normal or overstorage.

Thus it would appear that, whether or not, the active principle, Alpha iodine of the thyroid, ever becomes of great therapeutic value, though this is highly probable, its discovery and isolation have

added the needed conclusive evidence to prove the theory that hyperplastic toxic (exophthalmic) goiter is due to overfunction and overelimination in the thyroid. We hope in time to be able to show its further relationships, if they exist, in the production of symptoms of non-hyperplastic toxic goiter, and the absence of toxic symptoms in non-hyperplastic atoxic (simple) goiter. At present we are especially concerned with its activity on muscular tissue, and it is this phase of the study which has led us to investigate the changes in the myocardium in cases of goiter.

CLINICAL EVIDENCE OF MUSCULAR INVOLVEMENT IN GOITER

The clinical evidence of involvement of the skeletal muscles in hyperplastic toxic (exophthalmic) goiter has long been well recognized. This is most marked in the evident weakness of the quadriceps extensor, as shown by the patient's weakness in raising the feet to go upstairs, or to mount the step of the examining table. It is shown also in the very frequent evident weakness of the intercostals, and in the apparent weakness of the diaphragm, as exhibited in the hurried, shallow respirations of patients with exophthalmic goiter. It is probable also that one of the two large factors in the production of exophthalmos itself is the weakness and relaxation of the recti muscles of the eye. In the heart, tachycardia and cardiac dilatation have long been considered cardinal clinical symptoms in the syndrome of toxic goiter. Up to the present, however, no extensive studies have been made of the changes in the muscle-fibers and in their controlling nervous mechanism in goiter.

CARDIAC LESIONS

In a recent analysis of the lesions discovered in 1244 consecutive autopsies made in the Mayo Clinic, I was struck with the fact that the gross evidence of myocardial change had been noted in 71 per cent. of all cases of goiter, a percentage very materially higher than had been noted grossly in cases of cancer, 44 per cent., diseases of the respiratory system, 44 per cent., diseases of the liver and gall-bladder, 48 per cent., diseases of the genito-urinary organs, 49 per cent., and of syphilis, 60 per cent. Though these observations

were based on gross appearance alone, the lead of the goiter cases was very marked. But when we turn to the microscopic evidence of myocardial damage, we find that the percentage of involvement is even greater. Thus, out of 100 autopsies of cases of goiter the heart shows gross or microscopic lesions, or both, in the myocardium in practically every case.*

Histologically, the chief changes are shown in the myocardium in the very extensive fatty degeneration of the fibers. This is most marked in the preparations stained with Sudan III, and by silver impregnation methods. The fatty masses, when in small amounts, are collected in the fiber at the poles of the nucleus, and in many instances in which specific stains for fat have not been used, have been mistaken for extensive deposits of the "brown pigment of brown atrophy." When the degeneration is more advanced, the fatty deposits are found in large amounts more or less filling the whole muscle-fiber.

One of the most striking things in the study has been the discovery of sharp limitations of the fatty deposits to certain bundles of muscle. Where two or more bundles of muscle lie side by side, or superimposed over each other, it is common to find all the fibers of one bundle markedly infiltrated with fat, while those immediately contiguous to it are relatively or wholly free. At the outset this was sufficient to show the futility of cursory examinations of relatively small blocks of tissue removed at random from the cardiac wall. It is only by a careful study of sections accurately orientated with relation to their source from different muscle-bundles, and a comparison of the condition of these bundles in hearts from a large number of cases, that we may hope to arrive at any solution of the intricate problems involved. This will mean the detailed study of a large number of hearts, a study which is now in progress. So far I can report only that apparently most of the muscle-bands involved lie in the middle circumferential laminæ or in those next the endocardium. The muscle-bands next the peri-

* The tissue from a few of the autopsies made prior to 1910 was not available for the present study, owing to its loss of identity during accidental flooding of the museum at that time.

cardium are in general not nearly so much degenerated, though they may show, more than elsewhere, the segmentation and fragmentation so common in numerous other pathologic processes.

It is now fairly well established that Virchow's supposition is incorrect that the fat-droplets found within muscle-fibers are due to a change of the muscle-substance itself into fat. In other words, the so-called fatty degeneration of muscle is probably not, for the most part, if at all, a true fatty degeneration *per se*, but it is a rather fatty infiltration following a degeneration of the muscle-fiber. However, the essential fact for us to consider is that it does indicate a degeneration of the fiber, and consideration of the factors causing this degeneration is our next concern.

That the degeneration of the muscle-fibers of the heart is caused directly by the action of toxic substance on the muscle-fiber itself is rendered doubtful by the irregular distribution, which I have previously noted. It is difficult to conceive of a toxic substance circulating freely in the blood-stream, and thus carried to all probably equally exposed bundles of muscles of the heart, and yet affecting, and that intensely, isolated muscle-bundles, while others in immediate opposition thereto are affected but slightly or not at all. Clinically, also, it is difficult to see why any substance so circulating within the blood-stream should select certain of the skeletal muscles, as the quadriceps extensor, the intercostals, and the recti muscles of the eye, to the relative exclusion of the other skeletal muscles. While not denying the impossibility of such a selective action directly on the muscle-fibers, we have been led to look further for explanation of the phenomena in the possible involvement of certain nerve ganglia controlling muscular activity.

PART PLAYED BY NERVOUS SYSTEM

It is well known clinically that many vascularly distributed substances have a selective action for certain nerve ganglia, as witness post-diphtheritic paralysis, herpes zoster, etc. Surgically, it has been found that some reduction of exophthalmos may be produced by the excision of cervical sympathetic ganglia.

Recently, Durante and I have made a study of the cervical

sympathetic ganglia removed from 16 cases of goiter and as controls from a number of normal, both young and old, individuals, coming to autopsy. The evidence of destructive changes in the ganglion-cells in the cases of goiter is most marked in those in which the symptoms suggested the possible overactivity of the cervical sympathetic nerves, while, conversely, changes in cervical sympathetic ganglia removed from cases not clinically so affected show slight or no changes. These histologic changes consist in—(a) fatty deposits within the ganglion-cells indicating their previous degeneration; (b) atrophy and reduction in the number of ganglion-cells, and (c) diffuse fibrosis of the entire ganglion. Unfortunately, we have not been able to correlate these studies in cases of exophthalmos with histologic studies of the recti muscles of the eye in the same cases, since the eyes were not removed. However, autopsy material from exophthalmic goiter cases is gradually accumulating, and no doubt enough will be at hand ere long to form a basis for extensive investigation.

From work already done, the working hypothesis may be formulated that in hyperplastic toxic goiter the thyroid is first excited to overfunction by a stimulus originating in the gland itself or in the autonomic nervous system, that the excessive secretion of the overworking gland containing an abnormally large amount of highly toxic Alpha iodine is delivered into the circulation and finds its way (a) to certain selected ganglia of the sympathetic nervous system, thus stimulating muscular and glandular organs to overactivity, resulting in symptoms referable to such increased function, and in symptoms referable to the decreased function of such muscles or glandular organs which follows their inevitable degeneration from overwork; and (b) directly to the other non-skeletal tissues of the body, in some of which it produces a direct chemical change. Coincident with the degeneration of the muscle and glandular tissue there is probably also degeneration of the ganglion-cells controlling them. We must not overlook the possibility that the primary lesion in hyperplastic toxic goiter may be bacterial or other stimulation of the cervical sympathetic ganglia. Cannon's recent experiments in the production of many of the symptoms of hyperplastic

toxic goiter by crossed physiologic stimulation of the cervical sympathetic through its anastomosis with fibers of the phrenic nerve strongly suggest this.

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STUDIES IN BLOOD-PRESSURE

I. Blood-pressure and Thyrotoxicosis *

HENRY S. PLUMMER

In a paper presented before this Society two years ago the term "thyrotoxicosis" was applied to the constitutional state or states that may be associated with goiter. It was not my intention to include such definite pictures of hypothyroidism as myxedema and cretinism. Sufficient evidence was presented to demonstrate that exophthalmic goiter is a definite clinical entity, always associated with hyperplastic thyroid. To show this relationship, and for the reason that no definite relationship can be established between the various other pathologic pictures found in the thyroid and the constitutional states accompanying them, the following classification was tentatively used: (1) Hyperplastic toxic; (2) hyperplastic atoxic; (3) non-hyperplastic toxic; (4) non-hyperplastic atoxic.

Of the patients coming to operation, approximately 32 per cent. are hyperplastic and 68 per cent. non-hyperplastic.

Of the patients having hyperplastic goiter, 99.2 per cent. have toxic symptoms and 0.8 per cent. are atoxic. Very small areas of hypertrophy and hyperplasia are disregarded in this classification. Of the patients having non-hyperplastic goiter, from 20 per cent. to 32 per cent. are toxic, and from 68 per cent. to 80 per cent. atoxic.

The onset of exophthalmic goiter is relatively acute, and the course of the disease fairly definite. The order of onset of the more important symptoms, based on the average of our series, is as follows: (1) Mental excitation; (2) vasomotor disturbances; (3)

* Read before The Association of American Physicians, May, 1915. Reprinted from the Transactions of the Association, 1915, xxx.

tremor; (4) mental irritability; (5) tachycardia; (6) loss of strength; (7) cardiac insufficiency; (8) exophthalmos; (9) loss of weight; (10) diarrhea; (11) vomiting; (12) mental depression.

All of the associated facts make it seem probable that the syndrome accompanying hyperplastic thyroid is, in the main, attributable to a toxin in some way associated with a perverted, deficient, or excessive thyroid function. Assuming an overactivity, we can, for the purpose of associating our observation, in a general way point out the action of the product of this activity. The effect of small doses continued over a relatively short time is cerebral excitation, vasomotor dilatation, rise in systolic blood-pressure, stimulation of the heart, and general metabolism. Moderate doses cause cerebral irritability, mental and muscular incoördination, free perspiration, loss of weight, loss of strength, and cardiac insufficiency. Large doses exaggerate the preceding effects; mental depression follows cerebral irritability; vomiting and nausea result from a dose but little short of fatal. Relatively small doses continued over a longer period give rise to the evidence of more permanent types of damage, such as auricular fibrillation, hypertension, etc.

The degree of acute intoxication is indicated by the symptoms directly attributable to the nervous system, and the cardiac damage is, in a broad way, indicative of the degree of chronic intoxication.

Assuming the same toxin to be active in non-hyperplastic toxic goiter, still smaller doses acting over a longer period may, without evidence of acute intoxication, lead to myocardial degeneration. The history and findings may not materially differ from those of myocardial damage arising from other toxins. May a smaller dose, insufficient to cause either symptoms of acute intoxication or myocardial insufficiency, lead to a cardiovascular syndrome, with high blood-pressure, and ultimately to a true arterial hypertension?

Most of the variations in the course and severity of thyrotoxicosis can be conceived by an equation, the factors of which are: the dose of the toxin, the length of its administration, and the general and local susceptibility of the person to the toxin. This concep-

tion in no way invalidates the possibility of an antitoxic action, relation of the thyroid to other ductless glands, more or less perversion of the thyroid secretion, etc.

Patients coming to operation with non-hyperplastic toxic goiter give a history of having first noticed the goiter at the average age of twenty-two years, and the evidence of intoxication at the average age of 36.5 years. The corresponding ages for hyperplastic goiter are respectively 32 and 32.9 years. Eliminating the cases in which there is definite reason for thinking that the hyperplasia was ingrafted on a preceding non-hyperplastic goiter, the average interval is only 3.5 months.

More than half of these patients seen in our clinic come under observation within a year after the onset of the symptoms. If the average course of the intoxication be represented by a curve, the greatest height is reached during the latter half of the first year.

Considered in the aggregate, hyperplastic goiter develops rapidly, leads to an intense intoxication, accompanied by marked disturbance of the nervous system and cardiac damage.

On the other hand, toxic symptoms develop in cases having non-hyperplastic thyroid only after the elapse of fourteen and a half years (average). Myocardial damage, on the whole, dominates the fully developed clinical picture. In a small percentage of cases the intoxication is of sufficient intensity to produce a syndrome simulating that of early mild, or atypical, but never that of frank, fully developed, exophthalmic goiter.

In 63 of the 916 cases of non-hyperplastic goiter coming to operation in 1914 an enlarged heart, with low blood-pressure, was noted. In at least 50 per cent. of these cases, considered individually, there was but little evidence to suggest thyroid intoxication except the associated goiter.

Many patients give a history dating back three, four, or more years to an indefinite onset of loss of strength, loss of weight, palpitation, etc., terminating in the evidence of cardiac incompetency that brings them to the Clinic for the resection of a goiter first noted twenty years before. Occasionally a severe thyrotoxic syndrome develops suddenly, as it were, from the dumping of a stored-up

toxin into the circulation. It is not my purpose to go into the various phases and types of thyroid intoxication further than to lead up to the suggestion that the non-hyperplastic thyroid may possibly be in some way associated with a chronic intoxication, and that the toxic agent may be active for years preceding the condition that we recognize as thyrotoxicosis. From this it is but a step to the conception that a still lower degree of intoxication might, in the course of years, lead to a cardiovascular syndrome with hypertension.

The average high systolic blood-pressure attending hyperplastic goiter is shown in Tables II, III, and IV. The high pulse pressure, with the well-known vasomotor phenomena in exophthalmic goiter, leads to the almost unquestionable conclusion that there is no vascular hypertension in this condition. The high systolic pressure is essential to the maintenance of a normal diastolic blood-pressure in these cases having a low peripheral resistance. In many cases even a normal diastolic pressure is not maintained. That the long-continued intoxication associated with the hyperplastic thyroid may lead to hypertension is probable. Evidence to show this will not be considered in this paper. On the other hand, an unduly open peripheral vascular system is occasionally present in patients recovered from exophthalmic goiter. The height of the systolic blood-pressure in exophthalmic goiter is somewhat indicative of the degree of intoxication.

Table II, giving the average blood-pressure readings for non-hyperplastic goiter cases by half decades, at once demonstrates the association of high systolic blood-pressure with this condition, unless there are in the series many cases in which the association of the goiter and the high blood-pressure is accidental. To be further assured of the association of high blood-pressure with non-hyperplastic goiter, the percentage of patients over forty years of age having a systolic blood-pressure above 160 was compiled for hyperplastic goiter, non-hyperplastic goiter, cholecystitis with stones, uterine myoma and syphilis, conditions all tending to produce high blood-pressure.

TABLE I.—1745 CASES OF NON-HYPERPLASTIC GOITER
AVERAGE BLOOD-PRESSURE—HALF-DECADES

AGES	CASES	SYSTOLIC BLOOD-PRESSURE AVERAGE	DIASTOLIC BLOOD-PRESSURE AVERAGE
10-15.....	15	118.5	72.5
15-20.....	63	120.7	77.7
20-25.....	128	123.1	80.2
25-30.....	190	123.8	80.5
30-35.....	235	126.9	81.2
35-40.....	253	134.9	83.6
40-45.....	246	136.4	85.2
45-50.....	214	145.8	87.3
50-55.....	204	150.2	87.1
55-60.....	131	152.6	87.5
60-65.....	47	160.7	88.6
65-70.....	13	164.6	83.3
70-75.....	4	166.2	87.5
75-80.....	2	166.0	65.0

TABLE II.—847 CASES OF HYPERPLASTIC GOITER
AVERAGE BLOOD-PRESSURE—HALF-DECADES

AGES	CASES	SYSTOLIC BLOOD-PRESSURE AVERAGE	DIASTOLIC BLOOD-PRESSURE AVERAGE
10-15.....	14	138.5	68.8
15-20.....	58	139.4	75.9
20-25.....	110	137.8	70.7
25-30.....	164	139.6	75.2
30-35.....	139	140.8	78.7
35-40.....	106	155.2	75.6
40-45.....	93	145.1	76.7
45-50.....	94	153.1	77.8
50-55.....	47	152.4	77.0
55-60.....	17	160.6	77.7
60-65.....	5	160.0	71.2
65-70.....	0	000.0	00.0

TABLE III.—PERCENTAGE OF PATIENTS MORE THAN FORTY YEARS
OF AGE HAVING HIGH BLOOD-PRESSURE

	CASES	SYSTOLIC BLOOD-PRESSURE ABOVE 150	SYSTOLIC BLOOD-PRESSURE ABOVE 160
		Per cent.	Per cent.
Hyperplastic goiter.....	117	47 +	34
Non-hyperplastic goiter.....	417	35	27
Cholecystitis with stones.....	289	..	18
Uterine myoma.....	100	25	15
Positive Wassermann.....	100	21	14

TABLE IV.—PERCENTAGE BY DECADES OF PATIENTS HAVING A BLOOD-PRESSURE ABOVE 160

	AGES					
	10-20	20-30	30-40	40-50	50-60	60-70
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Hyperplastic goiter	12	17	22	30	37	100
Non-hyperplastic goiter	1	2	7	21	31	20

Table IV shows the percentage of patients from the second to the sixth decade having systolic blood-pressure above 160. The average blood-pressure and percentages given in this paper, except those in Tables I and II, include only the patients operated on in 1914. The figures compiled for 1912 and 1913 cases, on which this paper was originally based, do not materially differ.*

That 27 per cent. of patients having non-hyperplastic goiter above forty years of age are accompanied by a systolic blood-pressure above 160 eliminates the question of an accidental association. This question has been checked by much data, the publication of which is unnecessary. Is this high percentage of cases having a high systolic blood-pressure due to the inclusion, in this series, of a large number of non-hyperplastic goiters accompanied by acute intoxication?

Further consideration of the relation of high blood-pressure to non-hyperplastic goiter is facilitated by grouping the cases of non-hyperplastic goiter coming to operation in 1914 as follows:

Group I.—Symptomatically negative, systolic blood-pressure below 160—582 cases.

Group II.—Symptomatically positive, systolic blood-pressure below 160—224 cases.

Group III.—Symptomatically negative, systolic blood-pressure below 160—36 cases.

Group IV.—Symptomatically positive, systolic blood-pressure above 160—74 cases.

* They are not published here, as they were not compiled on quite the same basis, and are not comparable without confusing explanation, and the 1914 statistics are more accurate. I will not encumber the paper with any discussion regarding the accuracy of the statistics further than to state that there may be an occasional high reading which would be much more than offset in the tables giving percentages by the inclusion of the non-operated patients having high blood-pressure.

Group I includes the cases in which there is little, if any, evidence of disturbed thyroid function. The average systolic blood-pressure, however, is high for the patients over thirty-five.

Group II includes the patients having a systolic blood-pressure below 160, diagnosed as toxic non-hyperplastic goiter. In this group are to be found many cases that some diagnosticians would include with the exophthalmic goiters.

Group III, symptomatically negative, systolic blood-pressure above 160. These cases came under observation without any notable complaint except the presence of the goiter. The findings range from little more than the high systolic blood-pressure to those of a well-developed cardiorenal syndrome.

Group IV, symptomatically positive, systolic blood-pressure above 160. While many of the cases in this group are markedly thyrotoxic, this can be excluded, and the symptoms definitely attributed to the high blood-pressure, cardiovascular or cardiorenal syndrome in 37.

Including the 37 cases in Group IV with Group III, systolic blood-pressures above 160 were noted without any tangible evidence of thyrotoxicosis in 18.1 per cent. of all patients over forty years of age. *This percentage seems to definitely establish the association of high systolic blood-pressure with non-hyperplastic goiter, unaccompanied by definite evidence of thyrotoxicosis.*

Of the 110 patients having a systolic blood-pressure of over 160, 30 had a diastolic blood-pressure above 105. While it may not be true of individual cases, there can be no doubt that this group with high diastolic readings has more or less permanent cardiovascular damage.

What the relation may be between these cases and the cases having a relatively low diastolic blood-pressure and a high systolic blood-pressure we have not sufficient evidence to answer. It was my purpose to present in this paper much evidence that seems to suggest that the high systolic blood-pressures, though often transitory, are due to the same factors that later lead to high diastolic blood-pressure and permanent cardiovascular changes. This leads into so complete an analysis of the material that I have found it

impossible to handle the necessary statistical matter in time for publication in this paper.

I wish to again call attention to the fact that the clinical syndromes associated with hyperplastic and non-hyperplastic goiter are, for the purpose of this article, in the main attributed to the products of an overactive thyroid only as a convenient hypothesis. However, the establishment of exophthalmic goiter as a definite entity associated with hyperplastic thyroid (Plummer); the rise and fall in the clinical evidence of intoxication, corresponding with the development and regression of the hyperplasia (Wilson); and the separation of a pure chemical compound from the thyroid (Kendall), having a physiologic action closely in line with that assumed for thyrotoxicosis, almost, if not fully, warrants accepting this assumption as an established fact for hyperplastic toxic goiter. (It is probable that all hyperplastic goiters are delivering a product above the normal.) The consideration of the clinical picture in all its aspects alone leaves but little room for doubt. That the same or a modified product is in some way associated with the thyrotoxicosis of non-hyperplastic goiter is almost equally well established. The facts suggest that the hyperplastic thyroid is constantly delivering this product into the circulation, while they offer the theory that the non-hyperplastic goiter may, relative to the demands, either retain or deliver its product, the periods of overdelivery leading to thyrotoxicosis.

If we associate the arterial hypertension with non-hyperplastic goiter, the problem becomes more complex, and it is perhaps best to stop with the conception that the thyroid is not properly performing its function. Returning to facts, I wish to emphasize the point that I have left open the question of the association of arterial hypertension and goiter.

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GOITER AND LIFE EXPECTANCY *

CHARLES H. MAYO

The apparent prevalence and increase in goiter have aroused much interest in the subject during the last few years. The serious consideration of the mortality incident to disease of the thyroid is a subject worthy of study. Recording the dangers of surgical mortality will be of general benefit, since in the report of operative deaths lies the best incentive to avoid the dangers, low though they may be, of late operation by early treatment. When surgery is indicated, an early operation will avoid both the long period of disability before operation, and the slow convalescence occurring after late operations.

Deficiency of Thyroid.—The defect of being born without a thyroid results in the unintelligent human dwarf who seldom reaches the age of puberty. These children are known as cretins, and may be somewhat benefited by thyroid feeding. Some cretins are born with a goiter of the fetal type. Such cretins receive benefit from gland feeding and may live for many years, the influence of the thyroid producing greater development of the body and some mental improvement. Most animals are fortunate in being endowed with a superabundance of each of the various duct and ductless glands, which permits a wide variation in their functional activity and also often permits the removal of large quantities of the glands without apparent loss to the system. It is estimated that the growing child needs one-third of the total thyroid generally found in normal persons, while the adult seemingly may maintain perfect health with one-sixth of the gland. A minute amount

* Read before the Medical Section of the American Life Convention, French Lick, Ind., March 3, 1915. Reprinted from the *Lancet-Clinic*, 1915, cxiv, 649-651.

of the secretion seems to act as a hormone which maintains the necessary stimulation of the other kinetic glands of the body with associated function. Some operators maintain that total removal of the thyroid in the adult is harmless and is indicated in disease conditions. It is probable in such cases that the minute amount of secretion necessary comes from an accessory or aberrant thyroid. We should caution against the total removal of the thyroid except in malignancy. The reports of the past indicate that the dangers of myxedema may be an early or late manifestation, but they are to be watched for and their evil effects provided against.

The four parathyroids so intimately connected with the thyroid in location and function should be preserved with equal care from injury at operation. Undoubtedly two, and possibly one, of these glands may be sufficient to maintain function; but the danger of creating a deficiency of thyroid and parathyroid secretion is doubled when the operation on the thyroid is extended to removal or partial removal of both lobes, unless care is exerted to keep in front of the posterior capsule. If accidentally removed, the parathyroids should be reinserted in an adjacent location in the field of operation. Thyroid and parathyroid feeding should be started with lactate of calcium to control spasm of the muscle. With actual loss of glands the outlook is serious. If due to loss of circulation, later improvement is to be expected. While deaths from tetany represent but a fraction of 1 per cent., even this slight mortality is unfortunate because it is usually preventable. It will take many years before a knowledge of these glands becomes crystallized through the results of various types of operative measures and of medical treatment considered in relation to the work of histologists, pathologists, and other investigators.

Infections.—Investigations of Rosenow and others who have made cultures of the crushed tissue of diseased thyroids show that bacteria can be cultivated from some of the glands. While very suggestive, the exact relationship of these bacteria to the disease has not yet been sufficiently investigated to make any assertions. Acute infections are very rare, as is also tuberculosis. A late manifestation of lues is probably a factor in more cases than is generally

supposed. The mortality from infections other than surgical is so slight as hardly to need consideration.

Degenerations.—Malignant degenerations are very rare; carcinoma is more frequent than sarcoma, while both together represent less than 1 per cent. of the operations on more than 1300 new cases of goiter seen at our clinic in 1914. Late operations for these conditions are hopeless. The symptoms of malignancy are extreme; there are density and irregularity of structure, with increase in the size of the glands. Such cases should be looked upon with marked suspicion and an early operation advised. If found malignant, a complete thyroidectomy is indicated. Secondary operations for recurrence are usually of but little benefit, and are only indicated when a roentgenogram shows that the lungs, in which the metastases usually occur, are free from such involvement.

Simple goiter or a simple increase in the size of the gland may occur at any period of life, but is quite common at puberty, then being known as the goiter of adolescence, an edematous, swollen gland containing watery colloid and gland secretion. Such a growth may consist of round and encapsulated adenomas, or it may be diffuse. When located as an intrathoracic or substernal goiter, the size may, by pressure, endanger life from suffocation. Such glands are subject to degeneration, fibrous, cystic, or calcareous. These conditions are often designated as types of goiter; in reality they are types of degeneration. There is, however, a change that occurs after many years in such glands which produces a train of symptoms not unlike the worst features of exophthalmic goiter, *i. e.*, myocarditis, degeneration of the nerve, nephritis, and general toxemia. Such cases are more fatal than the average exophthalmic goiter, and the degenerations being terminal do not permit as favorable a response to treatment as does exophthalmic goiter. The mortality in these cases from operation is not less than 5 per cent.

Plummer¹ calls attention to a point in support of this theory that, so far as I know, has not hitherto been made, namely, that a person, aged twenty-two years, with an adenoma of the thyroid, has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the syndrome associated with

hyperplastic thyroid that the best-trained diagnosticians are constantly confusing the two conditions.

"The intoxications from non-hyperplastic goiter may be divided into two merging groups: (1) A group in which the cardiac toxin predominates, in which the clinical picture closely resembles, and in many instances can not be differentiated from the cardiovascular complex resulting from alcoholic, luetic, septic, and other well-known toxins; (2) a group more closely approaching the picture of Graves' disease and including the cases that have been erroneously so diagnosed by the mass of the profession.

"The term thyrotoxicosis is here applied to the constitutional state associated with goiter. As a matter of convenience for quickly presenting the association of the clinical and pathologic findings, the constitutional symptoms accompanying goiter were attributed to a toxemia the result of a disturbed thyroid function. As a temporary expedient the cases were classified pathologically as hyperplastic and non-hyperplastic, and clinically as hyperplastic toxic, hyperplastic atoxic, non-hyperplastic toxic, and non-hyperplastic atoxic. The glands showing marked hypertrophy were included with the hyperplastic goiters. Following the classification for the 2917 new cases coming to operation between January 1, 1909, and January 1, 1913, 42.8 per cent. were hyperplastic, and 57.2 per cent. were non-hyperplastic. Of the hyperplastics, 99.2 per cent. were toxic and 0.8 per cent. were atoxic. Of the non-hyperplastics, 23.3 per cent. were toxic and 76.7 per cent. were atoxic."

Plummer shows that: "While the association of the constitutional symptoms with non-hyperplastic goiter involves to a certain extent a personal equation, this is to a limited degree true for the cases having hyperplastic thyroids. The estimation that 23.3 per cent. of the non-hyperplastic goiters were toxic was made on a conservative basis.

"Patients coming under observation with non-hyperplastic toxic goiter gave a history of having first noted the goiter at the average age of twenty-two years, and the evidence of intoxication at the average age of 36.5 years. The corresponding ages for hyperplastic goiter were respectively 32 and 32.9 years.

"That non-hyperplastic goiter was noted ten years earlier in life than hyperplastic goiter that fourteen and one-half years elapsed between the appearance of non-hyperplastic goiter and the development of notable toxic symptoms, and that the constitutional symptoms were noted but a few months later than the goiter in the patients affected with hyperplastic thyroid was alone sufficient to show that we were dealing with at least two distinct pathologic and clinical groups. That one was not the sequence of the other was self-evident."

The following table is valuable in showing the varying conditions of simple goiters which were seen at the clinic during the year 1914. It includes also the thyrotoxic (non-hyperplastic) goiters:

TABLE I (1914).—SIMPLE GOITERS BY DECADES WITH REFERENCE TO AGE

YEARS	FEMALE	MALE	TOTAL
From 1 to 10 years.....	1	0	1
" 10 to 20 ".....	36	14	50
" 20 to 30 ".....	164	16	180
" 30 to 40 ".....	247	33	280
" 40 to 50 ".....	210	24	234
" 50 to 60 ".....	123	19	142
" 60 to 70 ".....	19	9	28
" 70 to 80 ".....	1	0	1
	801	115	916

The age incidence and the relative proportion of males to females are of importance. Nine hundred and thirty-four operations were performed on the 916 patients, with five deaths, which occurred in patients with thyrotoxic degenerations.

Hyperthyroidism or Exophthalmic Goiter.—An oversecretion of the gland which may be more or less perverted occurs in exophthalmic goiter. The pathologic proof of this is in the hyperplasia which is always present in the thyroid. Such glands are dry, hard, and more beefy, since they consist of a greater number of cells without retention of secretion or deposit of colloid, as is noted in simple goiter. This hyperplasia may be throughout the gland or only in

parts of it. The excess of secretion produces a regular series of variable but marked symptoms, of which the following have been formulated according to their importance by Plummer.² * * *

Some cases run an acute course to death in the first month, a slightly larger number in the latter half of the first year, at which time the most marked effect is shown on the heart, liver, kidneys, and nervous system. It is during this period that the operative mortality is the highest. After the first year these cases fluctuate with severe exacerbations, down to a base line which is far above normal. A few patients apparently make a fair recovery, with or without medical treatment, but relapse is common.

The following table gives the age incidence and proportion of males to females of the cases of exophthalmic goiter seen during the year.

TABLE II (1914).—EXOPHTHALMIC GOITERS BY DECADES WITH REFERENCE TO AGE

YEARS	FEMALE	MALE	TOTAL
From 1 to 10 years.....	1	0	1
" 10 to 20 ".....	31	3	34
" 20 to 30 ".....	104	18	122
" 30 to 40 ".....	95	17	112
" 40 to 50 ".....	64	19	83
" 50 to 60 ".....	26	5	31
" 60 to 70 ".....	2	1	3
	323	63	386

During the year 1914 there were 386 patients with hyperthyroidism given operative treatment, the number of operations greatly in excess of patients, since there were 22 injections with hot water (Porter's plan) with 2 deaths, 19 double ligations without mortality, and 388 single ligations with 2 deaths.

Percentages of Cured.—From a surgical standpoint operations, often aided by medical treatment, cure exophthalmic goiters in about 70 per cent. of cases; that is, the patients feel well, are able to carry on the ordinary business affairs of life, and forget that they have been sick, although 20 per cent. still show slight widening of

the palpebral fissure, which, while not realized by the patient, is noticeable to the trained physician. About 16 per cent. of the remaining patients are notably improved, but not well, having some symptoms that remind them of the necessity of being careful. About 4 or 5 per cent. have been operated on when the degeneration of the essential organs of the body had become permanent and there was hope of but little improvement, but the progress of the disease has been checked. In younger persons, about 5 per cent. with the same type of degeneration slowly make a partial recovery on account of their youth.

We think it would be fair to place the immediate mortality in exophthalmic goiter at about 3 per cent. This is not including our own cases, which in 1914 numbered 1302 (386 exophthalmic and 916 simple). In this number there were 278 consecutive patients operated on without a death. About 2 per cent. die of degenerations incident to the disease or of lowered vitality, due to the disease and some intercurrent trouble, within six months following operation. The mortality in simple goiter without complications is largely due to surgical accidents and need scarcely be considered. The mortality in degenerating simple goiter, the so-called thyrotoxic goiter, is high; we place it at least 2 per cent. greater than exophthalmic goiter.

Percentage of Relapses.—Relapses occur in about 10 per cent. of cases of exophthalmic goiter. These require the removal of a portion of the remaining lobe. The mortality from secondary operations is exceedingly low, since patients are greatly improved over their previous condition.

There is a relapse of an appreciable degree in about 10 per cent. of the cases of degenerating simple goiter. This is more especially true when the whole of one lobe has been removed instead of dividing the isthmus and taking the interior out of each lobe. About 5 per cent. of patients have secondary operations.

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RESULTS OF OPERATIONS FOR EXOPHTHALMIC GOITER*

EDWARD S. JUDD AND JOHN D. PEMBERTON

In this review of cases of exophthalmic goiter we have endeavored to ascertain as nearly as possible the results of operation for the condition. As is well known, it is difficult to determine when a condition of this kind is cured, and that some of the patients who are apparently cured may ultimately have relapses. In order that a sufficient length of time should have passed since operation, only the patients operated on in 1909 and in whom a definite diagnosis had been made were selected for this study.

In these cases the diagnosis of exophthalmic goiter was based on the clinical history and the histologic changes in the tissues when a part of the thyroid was removed. In a certain number no tissue was removed, ligation of the thyroid vessels only being done. In most instances, however, the thyroid was resected. The cases were all in the hyperplastic, toxic group, as described by Plummer and Wilson. (There was a definite so-called hypertrophy in all of the thyroids removed which was diagnosed by the clinician as exophthalmic goiter and by the pathologist as hyperplastic thyroid.)

Of the 176 patients in the series operated on in 1909, we have been able to trace 121 by correspondence and subsequent examinations. A number of these have returned several times for examination, and many of them have reported by letter several times.

It has been our custom to ligate the superior thyroid vessels in two types of exophthalmic goiter cases. In one type the disease

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was mild and we hoped the procedure might be sufficient to effect a cure. In the other type the disease was severe, and one or more ligations were done as a preliminary to resection. These patients were advised to return in three months for the removal of a part of the gland, but some of them were so greatly improved by the ligations that they did not return. Of the 121 patients that were traced, 56 were ligated; 36 had primary resections of the thyroid; 20 had preliminary ligations, followed later by resections. Nine of these patients were operated on for recurrence, at which time either one of the vessels was ligated or a part of the remaining piece of the thyroid was resected. The patients have been classified in five groups.

Group I.—In this group there were 55 (45.4 per cent.) patients cured; *i. e.*, those who had been well for some time, and, as far as they knew, or as we could judge, were completely relieved of all their former symptoms. In 16 of the 55 primary resections had been done; in 11 resections following ligations; in 24 ligations alone; and in 4 secondary ligations or resections following resections. We believe that the preliminary ligations should nearly always be followed by thyroidectomy, and that when ligations alone are done, late recurrences are much more common. On a number of occasions we have done thyroidectomies for the recurrence of symptoms after patients had been well for more than five years following ligation. One patient in this group was well for more than five years after the ligation of both superior thyroid vessels; then all the symptoms of hyperthyroidism gradually returned and the gland was resected. The following histories are illustrative of the cases in this group:

A30,233.—Mrs. A. M. B., aged twenty-seven years. Examination October 18, 1909. Acute symptoms of hyperthyroidism began about five and one-half years before. Enlargement of the thyroid was first noticed five years before. Six months before the appearance of the goiter she began to lose weight, was restless, irritable, and had slight tremor and general nervousness. Pulse 60. Two weeks after the goiter appeared there was a rather sudden onset of tachycardia with diarrhea. Pulse 170. There

had been nausea and vomiting and edema of the feet for six weeks. All the symptoms, except gastro-intestinal, had continued for two years. She was exhausted, unable to work, and lost 20 pounds during this time. During the last three years there had been gradual improvement. At the time of examination the pulse was 130; there was dyspnea, exhaustion on exertion, and restlessness. There was very little change in the size of the goiter—if anything, it was a little smaller. She had some difficulty in swallowing. Electric treatments had been given. The thyroid was firm, the right lobe larger than the left. The heart was regular and not enlarged. Her strength was fair, and nutrition good. The exophthalmos which had existed for five years was quite marked, uneven, more noticeable on the right side.

On October 20, 1909, the right lobe and isthmus were extirpated. The pathologist reported hyperplastic thyroid. The patient had a normal convalescence and left the hospital in a few days. She was the wife of a physician and we were thus able to follow her condition accurately. One year after the operation only a slight trace of trouble remained. Four years later her husband reported that she was entirely well, though the right eye was still a little more prominent than the left. At the present time she is entirely recovered and there is no evidence of her old trouble. In a letter she stated that it was about two years after the operation before she considered herself well. She now works with perfect ease. Her pulse is about 80. She has gained about ten pounds in weight. Her voice is clear. She is, in fact, in splendid health.

A29,110.—Dr. N. B., male, aged twenty-seven years. Examined September 17, 1909. The goiter was first noticed two years before. Hyperthyroidism probably started at about the same time. A small nodule in the right lobe of the thyroid was first noted; since then there have been tachycardia and some loss in weight and strength. From that time palpitation, tachycardia, and loss of weight has been variable. He had spells of diarrhea for two or three days at a time, sweating profusely. He first noticed exophthalmos about six months before. Tremor was not noted until a few months before, since then the symptoms gradually became more severe. The thyroid was rather soft, and the right lobe somewhat larger than the left. There was slight enlargement throughout the gland. The heart was normal in size. The pulse was 120, soft, and slightly irregular. The white blood-count was 6320; total lymphocytes, 49 per cent.

Operation September 20, 1909. Extirpation of the right lobe and isthmus. Pathologic report: hyperplastic thyroid.

One year after the operation this patient reported that he was much improved, thought here was still slight evidence of the old trouble. Six months after the operation he had had a relapse of the tachycardia, but this cleared up in a few months. He can now do as much work as he could before the beginning of his trouble. The exophthalmos has entirely disappeared. Present average pulse-rate, 85; normal weight before his trouble began was 150 pounds; present weight is 165 pounds. His voice was not affected by the condition.

A20,797.—F. E. K., male, aged forty years. Examination March 2, 1909. The goiter was noticed nine months before, though there may have been some evidence of hyperthyroidism for two years. He had an acute illness two years before which was called grip. He had been a little nervous for years, and thought that his present trouble has been coming on gradually for several years. He had lost 30 pounds in weight and complained of weakness, nervousness, and dyspnea on exertion. There had been no vomiting or diarrhea. Examination showed a hard gland, generally enlarged. No dilatation of the heart and no evidence of myocarditis. Pulse 120 to 130. Exophthalmos regular and quite marked. The first operation was done March 6, 1909, when the right lobe and isthmus were extirpated. After this he felt fairly well when resting. He grew stronger, less nervous, and gained 10 pounds in weight immediately after the operation, but lost it after working two weeks. When he returned for examination October 22, 1909, his pulse was 120. During August and September he had about ten attacks of biliary colic, with diaphragmatic spasms, and was obliged to take morphin several times on account of pain. October 29, 1909, the left lobe was resected. The pathologic report on both pieces of tissue was hyperplastic thyroid.

This man reports that about eight months elapsed after his second operation before he considered himself entirely well, but he is as well as before he began to have the trouble. He can now do his work with ease. The prominence of his eyes has disappeared. He regained the 30 pounds in weight and now weighs 150 pounds. This patient has recently undergone a successful operation for gallstones.

A26,401.—A. M., female, aged sixteen years. Examination July 17, 1909. Goiter first noticed one and one-half years

before. She had been nervous for several years and had noticed tremor. There had been a gradual onset of symptoms of hyperthyroidism, tachycardia, dyspnea, palpitation, loss in weight, etc. Ten months before the symptoms had been severe, and for several weeks she had been unable to be on her feet for any length of time. She had spells of diarrhea lasting three or four days at a time and several spells of nausea and vomiting. Exophthalmos for eleven months. The thyroid was enlarged; thrills distinct; the left lobe larger than the right. The heart was dilated $1\frac{1}{4}$ inches to the left. There was a systolic murmur at the apex. The pulse-rate was 150 and full. The white blood-count was 8000; total lymphocytes, 42 per cent. Operation July 29, 1909: ligation of both superior thyroid arteries.

This patient writes that she is much stronger than at any time before she had the trouble. There has been no recurrence of symptoms and she can do more work than before. The prominence of her eyes has gradually diminished; the appearance of her neck is normal. Pulse 80; hands steady. She has not taken medicine since her operation. She thinks that about six months elapsed before she was entirely well.

A27,574.—Mrs. A. O. M., aged thirty-four years. Examination August 1, 1909. This patient had a goiter at the age of eighteen which disappeared. Her mother had one at twenty and it disappeared. The second goiter was first noticed about a year ago. Symptoms of hyperthyroidism, tachycardia, nervousness, and enlargement of the thyroid had persisted for about five months. There was an irregular nodular enlargement of the gland. The heart was not dilated; pulse, 110 to 120. There was some prominence of the eyes. The white blood-count was 9200; total lymphocytes, 47 per cent. Operation August 18, 1909; ligation of the superior thyroid vessels. For more than two years after this, during which time she gave birth to a child, she felt well. In January, 1911, she returned, stating that for two months she had been having palpitation, dyspnea, and nervousness, though not nearly as severe as before the ligation. She had lost 17 pounds in these two months. On January 10, 1911, the right lobe and isthmus were removed. Pathologic report: hyperplastic thyroid.

She now reports that she is well. She thinks it was about six months after the second operation before she was entirely well. She had a few slight temporary attacks of palpitation and nervousness. The prominence of her eyes has diminished. The pulse was 68. Normal weight before her first symptoms was 110; just pre-

vious to the thyroidectomy, 98; present weight, 124. She had no trouble with her voice. Her husband, who is a physician, writes that in his opinion she is as well now as before the beginning of her illness.

Group II.—In this group of 22 patients (18.1 per cent.) all were practically cured of their symptoms, but still at times had slight evidence of the disease. Many of these are entirely well, though occasionally, under sudden nervous strain, they show that they are not entirely normal. In this group there were 11 primary resections, 4 resections following ligations, 6 ligations, and 1 secondary resection. Some of the case histories are given as typical of results in the group.

A27,928.—Mrs. A. A., aged twenty-eight years. Examination August 19, 1909. The goiter was first noticed two years before; the hyperthyroidism probably started five months before, when the goiter rapidly increased in size. There was a sudden onset of typical hyperthyroidism, profuse sweating, rapid loss in weight, etc. Examination showed the thyroid generally enlarged, bruit and thrill marked over arteries. Pulse 160. Exophthalmos marked. Long, harsh systolic murmur. On May 24, 1909, both superior thyroid arteries were ligated.

One year after the operation the patient wrote that she was apparently entirely well. She now writes that she is not quite so well; is nervous at times, but does not think there is any evidence of her old illness. Her general strength is improved, but she tires more easily than before she had the trouble. A slight enlargement in the region of the thyroid can be felt. Pulse 85; weight about normal. No tremor.

A30,012.—Mrs. J. M., aged fifty-four years. Examination October 11, 1909. This patient noticed the goiter four months before. Hyperthyroidism had probably lasted about eight months. She was weak and unable to do her housework. She lost about 50 pounds in weight. Tremor gradually became worse, now affecting her entire body. She was nervous and irritable and perspired easily. The thyroid was found generally enlarged, the right lobe larger than the left. It was firm, rounded, and regular in outline. The heart was slightly enlarged; the heart-sounds slightly deficient, regular at apex. There was a systolic murmur. The pulse was 120, regular, and of good quality. The white blood-

count was 9900; total lymphocytes, 35 per cent. Operation October 19, 1909: thyroidectomy; extirpation of the right lobe and isthmus. Pathologic report: hyperplastic thyroid.

This patient wrote that all of three years elapsed before she considered herself well, and at present her nervous condition is not good. However, there has been no recurrence and no evidence of the old trouble. Her strength has improved; she is able to do her housework. No exophthalmos. No tremor. Weight before the appearance of symptoms was 180; previous to the operation, 140; at present, 200 pounds. Her voice has not been affected.

A26,468.—D. B., woman, aged forty-three years. School-teacher. Examination July 19, 1909. The goiter was first noticed four months before, at which time symptoms of hyperthyroidism developed: palpitation, tachycardia, dyspnea, sweating. She complained of being hot; gradually developed tremor and diarrhea. There was no vomiting. The symptoms were progressive until May or the first of June, when they reached their height. For some six weeks she could hardly get about. She was treated by rest and gradually grew better. Exophthalmos was present. The thyroid was hard, with areas that felt cystic. The right lobe was considerably larger than the rest of the gland. The heart was dilated one-half inch to the left. There was a mitral systolic murmur. The pulse was 140, but with good tension. The white blood-count was 10,000; total lymphocytes, 30 per cent. On July 30, 1909, both superior thyroid arteries were ligated. She returned in May, 1911, stating that after the ligations she was in bed most of the time for three months because of palpitation and irregular heart action; since then she has been weak and unable to do much work. Palpitation occurs on excitement or exercise. Pulse from 80 to 90. Prominence of the eyes less. Operation May 15, 1911: thyroidectomy; extirpation of the right lobe and isthmus.

This patient reports that her nerves are not so strong as they were before her illness. She is troubled more or less with sleeplessness, but her general health has improved and she can work with more ease. The prominence of her eyes has disappeared; there is no enlargement of the neck. Average pulse, 80. No tremor. Normal weight, 100; previous to operation, 75; present weight, 100. She cannot use her voice as well as before.

Group III.—In this group of 7 patients were those who reported that they were markedly improved, but most of the time

there was some evidence of the old trouble, and those who retained a little exophthalmos or nervousness. Most of them had entirely regained their normal weight and physical strength. Of the 7, 3 had been simply ligated. In all probability if these 3 patients and the 6 in Group II who had simply been ligated would have resections now, the few remaining evidences of the disease might entirely disappear. One of the patients in Group III had a primary resection; 1 had a resection following ligation; and 2 had secondary resections. A typical case is as follows:

A28,982.—N. M., female, aged twenty-four years. Examination September 14, 1909. There had been gradual onset of nervousness, tachycardia, dyspnea, sweating, etc., several years before, and the patient had stayed in bed the greater part of a year. She then improved until within the last three months, when she became gradually worse. There was a firm prominence of the right and left lobes of the thyroid. Marked bruit of the upper poles. Heart regular; not dilated. Pulse 140. Marked systolic murmur at the apex. Exophthalmos quite marked. White blood-count, 6000; total lymphocytes, 33 per cent. Operation September 22, 1909: ligation of both superior thyroid arteries.

Recent report states that she has never considered herself entirely well, though her strength has gradually improved. Pulse, 92. There is some tremor; shortness of breath. Normal weight before her first symptoms, 115 pounds; present weight, 112. She has had an attack of jaundice, with rheumatism and gastric disturbance, since her operation.

Group IV.—In this group we have placed 5 patients in whom there was slight improvement. In 1 a simple ligation had been done, and this patient might now receive considerable benefit from a resection. As a rule, marked benefit follows ligation; if not, cure should not be expected in case the patient should have a thyroidectomy. Of these 5 patients, 3 had primary resections, and 1 was operated on a second time, with little or no improvement. The following case represents this group:

A23,024.—Mrs. A. G., aged forty-three years. Examination April 30, 1909. Hyperthyroidism had existed for five years. She

visited our clinic in 1904, when the diagnosis of Graves' disease was made. She was weak at that time and did not stay for treatment. She improved following this attack, and her condition continued to be nearly normal for about a year. One year prior to her second examination she began to lose weight rapidly (15 pounds). After three or four months she again improved and was fairly well until April of the following year, when she had a spell almost as serious as the first one. Exophthalmos at that time was quite marked. There was considerable enlargement of the right lobe of the thyroid, and slight enlargement on the left side. The heart was irregular in rhythm and force and was dilated $1\frac{1}{4}$ inches to the left. The pulse was regular—114. The white blood-count, 5700; total lymphocytes, 36.6 per cent. August 5, 1909, double ligation of the superior thyroid vessels was done. August 26, 1909, the right lobe was extirpated.

This patient writes that she is not as well as she was before her original attack; her strength has improved, but her general health is not good. Pulse, 80. No tremor.

Group V.—The 8 patients in this group derived little or no benefit from the operation. One had a primary resection, 1 a secondary resection, and 6 were simply ligated. The following history is representative of this group:

A27,142.—Female, aged nineteen years. Examination August 3, 1909. This patient had noted nervousness, not marked, for about three years. For the past nine months she had been easily exhausted. There were increased dyspnea, nervousness, and difficulty in getting up stairs. She had two or three spells of vomiting; was frequently nauseated; her feet were swollen. The thyroid was found moderately hard and nodular. There were thrills over the superior thyroids. The heart was slightly dilated. The pulse was 144 and there was some exophthalmos. The white blood-count was 6200: total lymphocytes, 34.9 per cent. Operation August 5, 1909; ligation of the superior thyroid vessels. May 9, 1910: thyroidectomy; extirpation of the right lobe and isthmus.

This patient has not been as well as she was before the beginning of her illness. Her general health improved for a time, but there has been a recurrence of the former symptoms. The eye prominence diminished for a time and again returned. Pulse 118 and irregular. There was tremor and some hoarseness.

In addition to the 121 patients, 3 others were traced, but sufficient data to classify them were not obtained. Patients who are benefited, but not cured, by the removal of a part of the thyroid will, in many instances, improve greatly with a resection of the remaining part of the gland. This point has been demonstrated in 9 of our patients in whom the symptoms recurred and the second operation was done. Of these 9 patients, 4 were cured by the secondary resection; 1 was practically cured, though slight evidence of the disease remained; 2 were greatly improved. These results tend to bear out the impression that if the patients are not cured it is because enough of the gland has not been removed.

An effort has been made to determine the factors pertaining to exophthalmic goiter which would indicate the results from operative treatment that might be promised patients. In this, however, we have been only partially successful. In eight of a group of 13 unsuccessful cases there was considerable dilatation of the heart at the time of operation, and several of the patients had developed edema. A complete cure could not be expected in this type of case; nevertheless, in several instances great benefit was derived from the operation. Twenty-five of the 55 patients who were cured had some dilatation of the heart at the time of operation.

The oldest patient operated on (fifty-seven years of age) and the youngest (four years and two months) were cured. The average age of the patients cured was 30.7 years; the average age of patients deriving little or no benefit was 29.1 years.

In the series of 121 patients traced there were 107 females and 14 males. All but 2 of the males were benefited. The average length of time in which these patients had had symptoms before coming for treatment was about the same in the group of cured (19.3 months) as in the group receiving no benefit (22.2 months). The average length of time required to effect a cure was 17.9 months. In the second and third groups, in which were included the patients who were better but not cured, the average length of symptoms was longer: in Group II, 31.6 months; in Group III, 49.2 months. Despite the fact that the statistics do not emphasize this point, we believe that more cures and better results will

be obtained in patients having symptoms for short periods than in those having symptoms for a number of years. The average duration of symptoms in patients who were cured was 19.3 months. It would seem reasonable to assume that if patients could have been treated within the first year, a larger percentage would have been cured.

All these patients had some degree of exophthalmos (Stellwag or von Graefe) before operation; many of them complained of pain and tension of the eyes, which usually disappeared soon after operation. Often they stated that their eyes felt much better even before there was any appreciable change in the degree of prominence. From our observations it would seem that the exophthalmos is one of the last symptoms to subside; sometimes it persists long after all other evidence of the disease has cleared up. Seventy-five patients reported that all prominence of the eyes had disappeared or was greatly diminished.

The functional results in our cases have been very satisfactory. A low collar incision just above the clavicle reflecting the superficial tissue flaps, severing the muscles just below their upper attachment on either side, if necessary, is inconspicuous. This incision heals quickly and normal motion of the head and neck returns in a few weeks. In a small number of patients there has been some disturbance in the voice, though this has been temporary. It is apt to be most marked about the fourth or fifth day, when the edema is greatest. In one instance there was total loss of the voice for two months, when it rapidly returned to normal. The characteristic squeaky goiter voice so often heard in exophthalmic patients before operation usually completely changes to normal by the time the wound has healed. Some of our patients who speak with the normal motion of the vocal cords have complained of the voice being weak or tiring easily. At times it is husky, and there is difficulty in singing. These symptoms usually subside in a very short time.

Of the 176 patients operated on in 1909 (some had three operations), 21 died, 7 in the hospital. All were females: the oldest, forty-six years, the youngest fifteen. In 5 a single ligation

only was done; in 2 there were resections. The average length of time symptoms had existed prior to operation was 29.5 months. One of the patients who died following resection had had a ligation and seemed entirely well. About five years after the ligation in our clinic she had a hysterectomy performed elsewhere. The goiter symptoms recurred, growing gradually worse, and she returned to us for resection.

The histories of the patients who died show that they were all operated on at the time of the maximum severity of the disease. If we had realized then as we do now the danger of operative interference at the height of any attack of hyperthyroidism, the patients might have been carried past the period of maximum severity before operating. In all these patients hyperthyroidism was the clinical diagnosis of the cause of death; 4 showed dilated hearts and edema. The average loss of weight of the 7 patients at the time of operation was 42 pounds. The average white blood-count was 7800, and the average lymphocyte count, 49.3 per cent.

Fourteen patients have died since leaving the hospital—one ten months after a double ligation. This patient had a recurrence of the trouble; was operated on elsewhere and died. The average length of time between operation and death in these 14 patients was 14.1 months. In 11, ligations were done; in 2, resections; and in 1 there was a recurrence. The average age was 34.1 years. Eleven had dilated hearts; four systolic murmurs. There was edema in 6 and evidence of nephritis in 4. From this review of the histories of patients who have died it seems evident that the condition was extremely toxic. It is quite probable that most of them died because of continued intoxication, which had produced irreparable damage, usually in the heart, liver, and kidneys.

Better judgement as to what should be done and when to do it has lowered the mortality considerably in the past five years. In the series of letters received from exophthalmic goiter patients during the past few months, eleven mention having borne healthy children since operation. One woman had had three children. In two pregnancies one patient had had a recurrence of all the symptoms of hyperthyroidism and, because of this, abortions had been

performed. This patient's report did not make clear that she was really suffering from hyperthyroidism when pregnant. Her chief symptom was vomiting, and this, of course, may have been the pernicious vomiting of pregnancy; however she had had one normal pregnancy without serious vomiting before her attack of hyperthyroidism. Eight of the women who have had children since operation have been classified in Group I as cured; two of them in Group II as improved; and one in Group III in which no benefit has been derived from operation.

Judging the results in this series of 121 patients, a cure may be expected in about 45 per cent. In addition to this, about 23 per cent. will be practically cured, although a slight trace of the old trouble may persist. Our statistics show that an additional 4 per cent. obtained some benefit. About 5 per cent. reported that they had received no benefit.

MEDICAL TREATMENT OF DIABETICS PRE- PARATORY TO SURGICAL TREATMENT *

DAVID M. BERKMAN

In the consideration of this subject it is not my intention to enter the field of general diabetic therapeusis, but merely to take up the possibilities of this condition and to discuss the means whereby the benefits of surgery may be extended to a larger number of patients already suffering from glycosuria, including even those in whom the surgical condition does not seriously threaten life or health.

During the last few years literature on this subject has been scant, although there have been numerous articles on the general treatment of diabetes. In 1902 Phillips¹ reported a large series of cases collected from the literature showing definitely the value of preoperative treatment. The mortality in cases without preoperative treatment was 36.37 per cent., as against 17.7 per cent. in treated cases. His classification, still in use, of diabetic patients with surgical conditions, is the following:

1. Glycosuria caused by surgical lesions.
2. Glycosuria causing surgical lesions.
3. Glycosuria and surgical lesions independent.
4. Glycosuria adding to the danger of surgical lesions.

Risley,² in a more recent article, quotes extensively from Phillips, and more clearly defines the limits of these four groups. He lays stress on the fact, which is now becoming generally accepted as a working base, that an arbitrary division between

* Read before the Minnesota State Med. Assoc., September, 1915. Reprinted from the *Journal-Lancet*, 1916, xxxvi.

glycosuria and diabetes does not exist, or, at least, must be ignored. Also, he properly calls attention to the fact that in the examination of urine the total output of ammonia and the presence of acetone bodies are of as much, if not greater, importance than the sugar itself, holding that not over one gram of ammonia should be excreted in twenty-four hours, while diacetic acid should be entirely absent before a patient is accepted as a fair operative risk.

Still more recently Addis,³ in an article on this subject, has shown the insignificance of the so-called dangers of sepsis and non-healing wounds in operating on diabetic patients as compared to the real danger of coma. He has called attention to the fact that coma occurs with equal frequency after operation on patients with marked and with mild glycosuria. As a basis for this, he quotes from Karewski, who operated on 136 glycosuric patients with a mortality of 20 per cent., 78 per cent. of which was from coma; of these, 50 per cent. were in so-called mild diabetics. Addis emphasizes the fact that a strict carbohydrate-free diet carried up to operation increases, rather than decreases, the liability to coma. He is working out a diet scheme which may be used as a functional test for fatty acid metabolism; and he believes that in this field lies the future practical test of the operability of glycosuric patients.

Allen's⁴ extensive researches have contributed to the advances in general treatment of diabetes; and the value of his methods seems substantiated by his results. Some of his opinions, especially concerning coma and its generative factors, appear quite radical and contrary to previously accepted ideas.

Transitory glycosuria is probably less frequent than the textbooks would lead us to believe, although often conditions are present which may have been the direct cause of glycosuria. The occasional appearance of sugar in the urine of an individual should be an indication for a careful general examination and continued observation over a period of years. Riesman⁵ has depreciated the influence of the thyroid in the production of glycosuria; and our experience would tend to bear out this view. He says that 10 per

cent. of pregnant non-diabetic women show glycosuria; and this appears to be a fair estimate.

The question of specific diet and relative food values and percentages is too extensive and intricate to enter into at this time. Among the most recent communications on this subject, the carefully detailed charts and therapeutic notes of Joslin⁶ are of great practical value.

The material for the present report was drawn from the histories of the patients operated on in our clinic during the past year in whose urine the presence of sugar was positively demonstrated. It has been our purpose to establish a method of determining the operability of such patients, and a reasonably rapid and safe course of treatment preparatory to and after operation. Our first object has been to render the patient's urine sugar-free as soon as possible; and for this no better procedure has been found than that advocated by Allen. An initial period of starvation of from forty-eight to seventy-two hours is instituted. During this period black coffee, small amounts of whisky three or four times a day, and all the water desired are allowed. A strict diet of meat, eggs, meats of nuts, and small amounts of cream, is then introduced. This is maintained until the urine is made sugar-free, and kept so for at least two days. Ordinary green vegetables of the 5 per cent. carbohydrate variety (Joslin) are then added until a fairly broad diet has been reached, still avoiding sugars, starches, and foods of every character rich in carbohydrates. The urine is, of course, carefully watched during the entire period; and, should sugar reappear, the diet is immediately cut down to the point of tolerance, and again brought up slowly. The physical condition of the patient, including the weight, is also the object of careful daily observation. The number of days that the urine should be kept free prior to broadening of the diet varies considerably, and is influenced by the nature and extent of the contemplated operation, the anesthetic to be used, the physical condition of the patient, and the influence which the diabetes has had on his previous health. It has not seemed that a strict diet, by merely rendering the urine sugar-free, decreased the risk of operation, but rather the contrary. We try

to increase the patient's tolerance so that he may have a larger power of utilization of the carbohydrates, which are gradually added to his diet. Thus he may come to operation with a greater reserve supply of glycogen, of which his body will be in very great need. Definite evidence of nephritis should be an absolute contraindication to operation, except when surgery offers the only hope of saving life.

Our use of sodium bicarbonate has become routine; and, despite the assertion of many that it is of little value, we feel that it has contributed in no small degree to the recovery of our patients. It is used in dram doses by mouth six to eight times daily, three or four days before the operation. This treatment is resumed as soon as possible after operation. Should the surgeon find it necessary to give rectal salines, soda is administered in this way also. We have on two or three occasions found it advisable to give it by intravenous injections in 5 per cent. solution.

The diet after operation requires more careful selection than before. The instability of the patient's appetite during this period and his physical condition often preclude the use of the coarser articles of food from which the diabetic diet is ordinarily selected. During the first forty-eight hours after operation, which is the most dangerous period, the patients desire little, if any, food. From that time on there is no definite rule to follow. Sugar must be excluded, and starchy food kept as low as possible, although it may be necessary to allow small amounts of milk, bread, and other food containing carbohydrates, in order to maintain nourishment and aid the recuperative power.

During the post-operative observation the urine is watched carefully, although keeping it free from sugar is more difficult, and is not so important as before operation. In the examination of the urine, twenty-four-hour specimens should be taken in every case, the points of special interest being the specific gravity, reaction, total amount of sugar in grams, total amount of ammonia in grams, and the diacetic acid. In estimating the percentage of sugar, we have used the polariscope, although the method is relatively unimportant if it is a standard one and is done by an ex-

perienced person. There are several methods for the determination of ammonia, the only points to be considered being simplicity and comparative accuracy. We have found no more suitable nor satisfactory method for the estimation of the diacetic acid than the universally used ferric chlorid reaction. The tests should be done in every case by the same person, so that relative accuracy may be obtained.

The danger-point in the ammonia output has been variously placed by different observers. The consensus of opinion is that it should be kept below one gram in twenty-four hours; however, one case running as high as 1.5 gm. and several running above 1 gm. have been operated on in our clinic. I have not found that an almost strictly protein diet will greatly raise the ammonia output, although it will cause, in almost every case, some slight increase. Operations have been performed, with slight trepidation, on seven cases showing diacetic acid, with no bad result. It would seem that the presence of a slight trace of diacetic acid is not an absolute contraindication to operation.

Gilfillan⁷ has warned us that when carbohydrates are withdrawn from the diet of healthy persons, acetone and diacetic acid may appear in the urine, but will disappear after a time. He has also emphasized the fact that the administration of alkalis will neutralize the acids formed in the blood, and will hasten their elimination, and that the addition of carbohydrates to the diet will tend to inhibit their production.

During the past year 26 glycosuric patients came to operation in the Mayo Clinic: 19 were women and 7 were men. The average age was forty-eight years, the oldest being sixty and the youngest twenty-one. Two patients died from operation, a mortality of 7.7 per cent. Eight patients were passing less than 10 grams of sugar in twenty-four hours on an ordinary diet; and, other conditions being satisfactory, they required very little pre-operative treatment, and that largely for the purposes of observation. Two received the bulk of their treatment elsewhere at diabetic sanatoria; the remainder were treated in our clinic. The character of the cases was as follows:

SURGICAL CONDITION	OPERATION	ANESTHETIC	NUM- BER OF CASES
Cyst of breast.....	Simple excision	Ether	1
Cancer of breast.....	Radical amputation	Ether	2
Right orbital cancer.....	Excision	Ether	1
Cancer of lip.....	Excision of lip and glands of neck	Ether	1
Duodenal ulcer.....	Gastro-enterostomy	Ether	1
Cholecystitis.....	Cholecystectomy	Ether	3
Cholecystitis and pancre- atic cyst.....	Cholecystectomy and drain- age of cyst	Ether	1
Fecal fistula.....	Dissection and closure	Ether	1
Cystic disease of cervix.....	Excision and cautery	Ether	1
Ovarian cyst.....	Abdominal resection	Ether	1
Hydrocele.....	Resection	Ether	1
Hypertrophy of prostate.....	Suprapubic stab and prosta- tectomy	Ether	1
Exophthalmic goiter.....	Ligation and thyroidectomy	Ether	2
Exophthalmic goiter.....	Ligation and thyroidectomy	Ether and novocain	1
Exophthalmic goiter.....	Ligation and thyroidectomy	Novocain	1
Exophthalmic goiter.....	Two single ligations	Novocain	1
Adenomas of thyroid.....	Resection	Ether	1
Adenomas of thyroid.....	Resection	Ether and novocain	1
Senile cataract.....	Extraction and iridectomy	Novocain	1
Perineal laceration.....	Perineorrhaphy	Ether	1
Umbilical hernia.....	Herniotomy.	Ether	1
Phimosis and hemorrhoids	Circumcision and cautery	Novocain	1
			26

The operation for senile cataract was performed with the patient passing 23.5 gm. of sugar and 1.5 gm. of ammonia in twenty-four hours, with a slight trace of diacetic acid. She made an uneventful recovery from her operation. Besides this patient, three others were operated on while still showing slight traces of sugar; another was passing 33 gm. of sugar, and still another passing 4 gm. The duration of the longest preparatory treatment was twenty-four days, the average length, fifteen days. Four patients gave a history of having previously had sugar in the urine; these four and one other gave a history of symptoms referable to diabetes extending over periods of from three months to three years.

One of the patients died after thyroidectomy, death occurring in coma within forty-eight hours of the operation. On first examination this patient was passing 90 gm. of sugar, and was looked upon as a typical diabetic; she was treated elsewhere, remaining

at a sanatorium on diet for two months prior to operation, and on her return was still passing 13 gm. of sugar. The urine was otherwise satisfactory. Her condition was believed to be serious enough to justify the risk of operation.

The other patient who died had been passing large amounts of sugar which cleared up readily with treatment. Operation revealed gall-stones and a large pancreatic cyst, two-thirds of the pancreas being necrotic and the condition of the remaining third doubtful. This patient did not die in coma; and the condition found at operation, together with the extent of surgery performed, would seem almost sufficient to cause death.

Of the 26 patients, 5 (4 exophthalmic goiters and 1 pancreatic cyst) may be placed in Group 1 of Phillips' classification; the remaining 21 without further postoperative data, which we have not at hand at this time, must be placed in Group 3. None of the cases falls into Group 2, and the entire series, according to one's interpretation, might be applicable to Group 4.

The fact that 5 of these patients were cases of exophthalmic goiter loses its significance; since in the routine twenty-four-hour urinalyses of 180 patients with exophthalmic goiter (October 1, 1914, to September 1, 1915) glycosuria was found in these 5 only (2.8 per cent.). With most other observers, I believe that the coma after operation will develop within forty-eight hours and that it is usually induced by the anesthetic. Ether in the hands of a skilled anesthetist is the safest and most flexible of the general anesthetics. Undoubtedly, local anesthesia, where possible, is directly indicated when glycosuria is present.

Much experimental work has been done, and considerable has been written, regarding the delayed healing of wounds and the frequent development of low-grade infection following operation on patients with glycosuria. In regard to this I can only say that, so far as can be determined, in not a single instance in our series has there been the slightest deviation from the average case in the healing of the wounds.

In spite of the increasing amount of experimental work done by those investigating the percentage of blood-sugar, the practical

applicability of this determination is still a matter of question. Bertrand originated a method for this determination which, on account of the large amount of blood required (10 c.c.), has been called the "macro-method." While possibly more accurate than most other methods, it has not been satisfactory because of the amount of blood used and the length of time necessary for the completion of the determination. To obviate these shortcomings, Bang produced a method called the "micro-method," which required a few drops of blood, and thirty-five to forty minutes only for its completion. This method is now quite generally used in laboratories throughout the country. Fitz⁸ compared these two methods in a series of cases, and describes the technic in full. Epstein⁹ has perfected a modification of a very simple method originated by Benedict, which requires only a small amount of blood and a few minutes' time. It is a color-comparison scheme, and the percentage is read off directly on an instrument resembling a hemoglobinometer. This method has been used in our clinic for several months; but, so far, efforts have been confined to developing the technic and establishing the approximate normal limits. We hope eventually to use the test routinely to detect the occasional patient in whom the amount of sugar in the urine, probably because of some obscure renal condition, is an unstable index as to the percentage of sugar in the blood.

While the results of treatment in this short series of cases has been fortunate, we are well aware of the serious nature of the condition, and are inclined to increase our precautions by insisting that patients be kept sugar-free for a longer period, gradually bringing them back to as near a normal diet as possible.

The treatment of the diabetic patient who is being prepared for operation is often difficult, and requires the absolute co-operation of the patient himself and of his immediate family. In many instances there has been no previous knowledge of sugar in the urine; and after operation these patients should be fully impressed with the seriousness of their condition and the necessity for continuation of the dietary treatment after their return home.

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THE RELATION OF THE ADRENALS TO THE PANCREAS *

FRANK C. MANN AND DELLA DRIPS

It was noted at autopsy, in a study of animals dying after the removal of both adrenals, that the pancreas always presents a characteristic appearance. In color the gland is deep pink and contrasts quite strikingly with the faint white color of the normal pancreas. Because of their marked injection it is possible to see all the vessels by transmitted light; even those leading to the small lobules stand out prominently. Histologically, the islands appear prominent and the capillaries are engorged with blood. This appearance is only slightly simulated by that of the fatigued gland at the end of a long period of digestion. Since these changes in the pancreas were so marked and constant, we deemed them worthy of a separate investigation. This seemed especially desirable as accurate data in regard to the polyglandular theory are very scant. We found only one reference describing a seemingly similar condition of the pancreas. Sweet and Allen¹ noted that at necropsy of dogs from which the hypophysis had been removed the pancreas presented a striking red coloration, like that seen at the height of digestion. Microscopic study, however, did not reveal any very marked changes.

Numerous experiments have been reported the results of which tend to establish the existence of a specific functional relationship between the adrenals and the pancreas. Hypotheses concerning this relationship are based on two facts: (1) That epinephrin produces glycosuria, and (2) that it decreases the flow of pancreatic juice. Investigation has failed to demonstrate that the glycosuric action of epinephrin is due to its primary effect on the pancreas. Lusk and Riche² conclude that the glycosuric action of epinephrin is due to vasoconstriction and not to inhibition of pancreatic func-

* Reprinted from Arch. Inter. Med., 1915, xvi, 681-692.

tion. Crowe and Wislocki,³ who recently investigated the subject, conclude that carbohydrate tolerance is not modified in an adrenalectomized animal. The most comprehensive work on the relationship of the adrenals to pancreatic secretion has been done by Pemberton and Sweet.⁴ They demonstrate that the injection of epinephrin decreases or inhibits the flow of pancreatic juice and that the removal of the adrenals increases the pancreatic secretion. From these observations they conclude that the adrenals have an inhibitory function over the pancreas. Edmunds,⁵ in a study of the effects of epinephrin on the flow of pancreatic juice, concludes that the inhibitory action is due to the production of marked vasoconstriction.

Two general methods were used to study the effect of adrenal insufficiency on the pancreas:

A. We performed a series of experiments in which the flow of pancreatic juice was carefully observed after various procedures on the adrenals. The experiments under this method may be considered in two general groups, the first comprising those experiments in which the flow was recorded in anesthetized animals, and the second those in which the flow was observed in unanesthetized animals.

B. By means of special stains, we studied the histologic changes in the pancreas after these procedures.

METHOD A.—FLOW OF PANCREATIC JUICE AND GROSS ANATOMIC CHANGES AFTER ADRENALECTOMY

Group 1.—The general procedure in Group 1 was as follows: All the animals were fasted for thirty-six hours prior to the time of experiment. They were carefully anesthetized with ether. Carotid blood-pressure was usually recorded by a Huertle manometer; however, the blood-pressure could be measured directly by means of a two-way stop-cock connected with a mercury manometer. All readings for blood-pressure were taken from the mercury manometer. The flow of pancreatic juice was obtained by placing in the major pancreatic duct a cannula connected with a glass tube graduated in 0.01 cm. Readings expressed in cubic centimeters were taken for fifteen-minute intervals. Blood-pressure

and flow of pancreatic juice were recorded hourly on an extension kymograph for a period of fifteen minutes. Normal temperature conditions were approximated as closely as possible by the judicious use of an electric pad. Since the passage of acid fluid from the stomach might prove to be a disturbing factor, the pylorus was usually ligated. In some experiments the minor duct was ligated to see if the free communication of the major and minor pancreatic ducts which is present in the dog was complicating results.

Series A.—In this series of five experiments the flow of pancreatic juice was measured in normal anesthetized animals, the experiments usually extending over eight to sixteen hours. In general, our results corroborated those of Pemberton and Sweet. In one animal there was no flow; in the others there was a slight initial flow, which increased as the blood-pressure decreased. The following is a representative protocol:

Experiment 4 (Series A).—October 5, 1914. Large male bulldog in good condition. Weight, 36 pounds. Had fasted thirty-six hours. Etherized at 7.30 A. M. Apparatus arranged to record carotid blood-pressure.

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
7.45 A. M.	180	42	100.9°	110	..
8.15 A. M.	180	42	98.2°	110	..
8.15-8.30 A. M.04
8.30 A. M.	180	42	98.2°	110	..
8.30-8.45 A. M.01
8.45-9.00 A. M.015
9.00 A. M.	156	48	97.6°	105	..
9.00-9.15 A. M.005
9.15-9.30 A. M.000
9.30 A. M.	144	48	98.6°	100	..
9.30-9.45 A. M.000
9.45-10.00 A. M.000
10.00 A. M.	150	42	97.3°	90	..
10.00-10.15 A. M.
10.15-10.30 A. M.000
10.30 A. M.	130	46	97.4°	85	..
10.30-10.45 A. M.000
10.45-11.00 A. M.000
11.00 A. M.	158	48	98.2°	85	..
11.00-11.15 A. M.000
11.15-11.30 A. M.000
11.30 A. M.	132	36	98.8°	90	..
11.30-11.45 A. M.05
11.45-12.00 A. M.04

* Cannula inserted.

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
12.00 M.....	180	42	101.2°	90	..
12.00-12.15 P. M.08
12.15-12.30 P. M.08
12.30 P. M.	180	42	101.4°	90	..
12.30-12.45 P. M.000
12.45-1.00 P. M.000
1.00 P. M.	180	42	101.2°	90	..
1.00-1.15 P. M.000
1.15-1.30 P. M.000
1.30 P. M.	180	48	100.6°	105	..
1.30-1.45 P. M.000
1.45-2.00 P. M.005
2.00 P. M.	156	48	100.6°	105	..
2.00-2.15 P. M.000
2.15-2.30 P. M.000
2.30 P. M.	156	48	101.6°	100	..
2.30-2.45 P. M.000
2.45-3.00 P. M.000
3.00 P. M.	180	60	101.8°	100	..
3.00-3.15 P. M.000
3.15-3.30 P. M.000
3.30 P. M.	180	60	101.8°	100	..
3.30-3.45 P. M.02
3.45-4.00 P. M.07
4.00 P. M.	180	60	101.1°	80	..
4.00-4.15 P. M.06
4.15-4.30 P. M.08
4.30 P. M.	180	48	101.2°	80	..
4.30-4.45 P. M.06
4.45-5.00 P. M.02
5.00 P. M.	180	48	101.9°	76	..
5.00-5.15 P. M.05
5.15-5.30 P. M.03
5.30 P. M.	180	36	102.2°	75	..
5.30-5.45 P. M.00
6.00 P. M.	180	36	102.4°	60	..
6.00-6.15 P. M.06
6.15-6.30 P. M.05
6.30 P. M.	180	42	101.6°	60	..
6.30-6.45 P. M.11
6.45-7.00 P. M.23
7.00 P. M.	180	42	101.0°	50	..
7.00-7.15 P. M.08
7.15-7.30 P. M.14
7.30 P. M.	150	42	100.4°	50	..
7.30-7.45 P. M.11
7.45-8.00 P. M.05
8.00 P. M.	180	36	100.1°	45	..
8.00-8.15 P. M.29
8.15-8.30 P. M.07
8.30 P. M.	150	30	100.1°	40	..
8.30-8.45 P. M.10
8.45-9.00 P. M.15
9.00 P. M.	180	36	100.6°	38	..
9.00-9.15 P. M.12
9.40 P. M.	Animal died.				

Necropsy.—Performed immediately after death. Pyloric ligature had held, allowing no leakage. Thick fluid in stomach, which was markedly acid. No food material found above colon. There had been no hemorrhage. All organs appeared normal grossly. The weight of the pancreas was 45 gm.

Series B.—In this series of three experiments, after taking a control flow of pancreatic juice, the adrenals were quickly removed and the flow recorded until death. Our results again corroborate those of Pemberton and Sweet, although the increase we obtained is not so pronounced as they record. The following experiment is typical:

Experiment 2 (Series B).—October 18, 1914. Large white bull in good condition. Etherized at 8.20 A. M. Considerable difficulty experienced in getting the cannula in the duct. Stomach not ligated. Normal pulse, 210; respiration, 42; temperature, 99.2° F., and blood-pressure 100 at 8.30 A. M.

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
9.15 A. M.	168	42	99.2°	85	..
9.30 A. M.	162	42	98.8°	95	*
9.15-9.30 A. M.02
9.45 A. M.	Right adrenal was taken out.				..
9.30-9.45 A. M.04
9.51 A. M.	Left adrenal was taken out.				..
9.45-10.00 A. M.05
10.00 A. M.	162	42	98.4°	95	..
10.30 A. M.	160	36	99.2°	90	..
10.45-11.00 A. M.01
11.00 A. M.	142	32	99.4°	100	..
11.00-11.15 A. M.04
11.15-11.30 A. M.03
11.30 A. M.	156	39	99.8°	105	..
11.30-11.45 A. M.03
11.45-12.00 A. M.05
12.00 M.	180	36	99.6°	105	..
12.00-12.15 P. M.09
12.15-12.30 P. M.11
12.30 P. M.	180	60	99.2°	105	..
12.30-12.45 P. M.12
12.45-1.00 P. M.10
1.00 P. M.	180	60	99.2°	65	..
1.00-1.15 P. M.	180	36	99.2°	60	.12

* Cannula inserted.

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
1.30-1.45 P. M.....18
1.45-2.00 P. M.....18
2.00 P. M.....	180	40	99.8°	50	..
2.00-2.15 P. M.....26
2.15-2.30 P. M.....22
2.30 P. M.....	180	42	99.9°	45	..
2.30-2.45 P. M.....23
2.45-3.00 P. M.....33
3.00 P. M.....	160	36	99.8°	40	..
3.00-3.15 P. M.....30
3.15-3.30 P. M.....25
3.30 P. M.....	132	34	100.2°	32	..
3.30-3.45 P. M.....30
3.45-4.00 P. M.....35
4.00 P. M.....	162	42	100.4°	35	..
4.05 P. M.....	Injected small amount of adrenalin, which increased the blood-pressure, but decreased the pancreatic flow.				
4.16 P. M.....	Injected nicotin, which decreased blood-pressure and pulse. Pancreatic flow decreased at first, but it soon quickened.				
4.22 P. M.....	Animal died.				

Necropsy.—Performed immediately after death. No hemorrhage at the sites of operation. Pancreas grossly normal. The stomach contained about 150 c.c. yellow colored fluid, acid in reaction.

Series C.—In this series of 12 experiments one adrenal, usually the right, had been removed some days previously. The remaining gland was removed through a lumbar incision at the time of observation. Blood-pressure was decreased but slightly by the adrenalectomy. In every experiment of this series the flow of pancreatic juice was increased after the removal of the remaining gland, but this observation is inconclusive, inasmuch as in many cases the increase was no greater than occurred in the control toward the end of the experiment. A typical experiment follows:

Experiment 7 (Series C).—October 7, 1914. Large white bull bitch of gentle disposition, whose weight was 11,942 gm. The right adrenal had been removed two weeks previously. The animal was in excellent condition. Fasted thirty-six hours prior to the experiment. Etherized at 8 A. M. and apparatus arranged to record blood-pressure and pancreatic flow.

Table as follows:

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
8.30 A. M.	180	60	98.2°	120	..
8.45 A. M.	168	60	98.2°	100	*
9.00 A. M.	168	66	98.2°	95	..
9.00-9.15 A. M.04
9.15 A. M.03
9.15-9.30 A. M.	The remaining adrenal removed.				
9.30 A. M.	174	60	98.0°	95	..
9.30-9.45 A. M.03
9.45-10.00 A. M.03
10.00 A. M.	150	54	95.2°	105	..
10.00-10.15 A. M.02
10.15-10.30 A. M.01
10.30-10.45 A. M.04
10.45-11.00 A. M.04
11.00 A. M.	150	54	95.2°	115	..
11.00-11.15 A. M.04
11.15-11.30 A. M.04
11.30-11.45 A. M.035
11.45-12.00 M.055
12.00 M.	144	48	94.6°	115	..
12.00-12.15 P. M.03
12.15-12.30 P. M.07
12.30-12.45 P. M.085
12.45-1.00 P. M.075
1.00 P. M.	150	48	96.0°	110	..
1.00-1.15 P. M.08
1.15-1.30 P. M.07
1.30-1.45 P. M.085
1.45-2.00 P. M.075
2.00 P. M.	150	48	96.1°	80	..
2.00-2.15 P. M.09
2.15-2.30 P. M.09
2.30-2.45 P. M.06
2.45-3.00 P. M.06
3.00 P. M.	120	24	96.1°	55	..
3.00-3.15 P. M.05
3.15-3.30 P. M.06
3.30-3.45 P. M.06
3.45-4.00 P. M.08
4.00 P. M.	204	42	97.0°	35	..
4.00-4.15 P. M.08
4.15-4.30 P. M.12
4.35 P. M.	Animal died.				

* Cannula inserted.

Necropsy.—Performed at once. Site of operation in excellent condition. No hemorrhage. No leakage through the pyloric ligature. Acid found in the stomach. All the other organs normal grossly. Weight of the pancreas, 35 gm.

Series D.—In this series of five experiments both adrenals were removed under sterile conditions, at the same time or at different operations. The pancreatic flow was studied after development of various degrees of adrenal insufficiency. We found that in an animal which had developed none of the symptoms of adrenal insufficiency the pancreas, while active, showed no increase over the controls. In every animal studied after the development of the signs of insufficiency, the pancreas was found to be secreting, but usually a scarcely appreciable amount. The following experiment is a record of the greatest flow obtained in this series:

Experiment 5 (Series D).—Adult male mongrel. On February 17, 1915, the left adrenal gland was removed. The animal quickly recovered from the operation.

DATE	TIME	PULSE	RESPIRATION	TEMPERATURE
March 1, 1915.....	5.30 P. M.	73	20	101.9°
March 2, 1915.....	8.00 A. M.	78	20	102.3°
	10.00 A. M.	Remaining adrenal gland removed.		
	3.30 P. M.	135	20	102.8°
	5.30 P. M.	142	21	103.2°
March 3, 1915.....	2.30 P. M.	142	20	103.2°
March 4, 1915.....	8.00 A. M.	150	22	103.1°
	9.30 A. M.	136	22	102.4°

Up to this time the animal appeared normal in every respect. Ate and drank regularly and showed no signs of muscular weakness.

March 4, 1915..... | 2.55 P. M. | 120 | 20 | 102.1° Normal data

ANIMAL ETHERIZED

3.00 P. M. | 175 Cannula in carotid; blood-pressure, 80.
4.15 P. M. | Cannula in main duct. Secretion slight,
blood-pressure, 50.

	TIME	PULSE	RESPIRATION	TEMPERATURE	PANCREATIC FLOW
	4.15-4.30 P. M.24
	4.30-4.45 P. M.17
	4.45-5.00 P. M.15
	5.00 P. M.	Animal bled to death from the femoral artery.			

Necropsy.—The pancreas was just beginning to become pink in color. The vessels were slightly congested.

Series E.—In this series of two experiments, after recording the normal flow of pancreatic juice, one adrenal was removed, leaving

the other intact. This procedure did not produce adrenal insufficiency, yet the increase in flow of pancreatic juice was just as great as in the instances in which both glands were removed. This fact is shown by the following experiment:

Experiment 11 (Series E).—April 9, 1915. Adult male poodle dog. Weight, 8200 grams. Was fasted for thirty-six hours prior to the operation. Pulse, 130; respiration, 24; temperature, 101.2° F. Normal blood-pressure, 144. Etherized at 7.45 A. M.

TIME	PULSE	RESPIRATION	TEMPERATURE	BLOOD-PRESSURE	PANCREATIC FLOW
8.00 A. M.	142	36	101.0°	144	..
		Abdomen opened and the minor pancreatic duct ligated. Cannula placed in the main pancreatic duct.			
8.30-8.45 A. M.02
8.45 A. M.	160	28	..	116	..
		Left adrenal removed.			
8.45-9.00 A. M.	98	.025
9.00 A. M.	173	56	100.2°
9.00-9.15 A. M.04
9.15-9.30 A. M.03
9.30 A. M.	216	52	100.0°
9.30-9.45 A. M.05
9.45-10.00 A. M.06
10.00 A. M.	814	48	100.1°
10.00-10.15 A. M.06
10.15-10.30 A. M.10
10.30 A. M.	180	39	100.0°
10.30-10.45 A. M.15
10.45-11.00 A. M.20
11.00 A. M.	240	42	99.8°
11.00-11.15 A. M.22
11.15-11.30 A. M.20
11.30 A. M.	240	54	104.0°	85	..
11.30-11.45 A. M.22
11.45-12.00 M.23
12.00 M.	240	48	104.6°	85	..
12.00-12.15 P. M.23
12.15-12.30 P. M.30
12.30 P. M.	268	72	103.4°	85	..
12.30-12.45 P. M.36
12.45-1.00 P. M.42
1.00-1.15 P. M.58
1.15-1.30 P. M.60
1.30 P. M.	270	52	103.8°	50	..
1.30-1.45 P. M.	Animal growing very weak.			40	..
1.45-2.00 P. M.	1.15
2.00 P. M.	240	38	104.2°
2.00-2.15 P. M.89
2.16 P. M.	Animal died.				

Necropsy.—Stomach almost empty, no free fluid, mucosa acid in reaction.

Group 2.—Method A.—The flow of pancreatic juice in unanesthetized animals was studied in one series of experiments. In three other series the condition of the gland itself was studied.

Series F.—In this series of five experiments a temporary pancreatic fistula was established in an animal in which one adrenal had been removed. The fistula was made under sterile conditions by securely fixing a glass cannula in the major duct, after ligating the accessory duct. After observing the rate of pancreatic flow, and when the animal had recovered from the effects of the operation, the remaining adrenal was removed and the animal observed until death. These experiments were more or less unsatisfactory because of clotting of blood in the cannula, infection and necrosis of the duct at the point where the cannula was tied. In none of these experiments was there an increased flow of pancreatic juice after adrenalectomy; however, in none of the animals did the pancreas have the injected blood-vessels and characteristic color as observed in the double adrenalectomized animal. The most important fact learned from these experiments was that the slight increase in flow noted in most of the anesthetized animals, after removal of the adrenals, was wholly insignificant when compared with the secretion of the gland during digestion. In the anesthetized animal the flow usually did not reach, and rarely exceeded, 0.05 c.c. in a quarter of an hour, while in unanesthetized animals, of approximately the same size, during the digestive period the secretion was as much as 1 c.c. per minute. This fact is emphasized by the following experiment:

Experiment 4 (Series F).—White and brindle male bulldog; old; very prone to fight. Right adrenal removed at 10 A. M., October 31, 1914. Wound kept in good condition. November 3, 1915, 10 A. M., the accessory pancreatic duct was ligated and glass cannula placed in main duct. Moderate secretion. Temperature of kennel remained at 70° F. The animal drank milk at 12 M.

DATE	TIME	PULSE	RESPIRATION	TEMPERATURE	PANCREATIC FLOW, C.C.
November 3, 1915..	2.15 P. M.	84	18	104.3°	6.80
	5.00 P. M.	120	12	103.0°	5.40
	6.10 P. M.	90	12	102.0°	3.75
	6.15 P. M.	Animal drank milk.			
November 4, 1915..	8.30 P. M.	90	12	102.0°	3.75
	6.15 A. M.	140	12	103.0°	1.15
	9.00 A. M.				12.0
	9.30 A. M.	Remaining adrenal removed. There was no flow of pancreatic juice after this time.			
	11.00 A. M.	156	30	102.0°	..
	12.00 M.	Animal drank milk.			
	2.16 P. M.	210	24	102.2°	..
	5.30 P. M.	168	18	103.0°	..
	9.15 P. M.	240	12	103.0°	..
Animal died during night.					

Necropsy.—The pancreas, aside from a slight congestion, seemed normal. Pancreatic cannula had ulcerated out of position.

Series G.—In practically all experiments, in anesthetized and unanesthetized animals, the contents of the stomach were found at autopsy to be acid. That the characteristic appearance of the pancreas, after removal of the adrenals, is not dependent on the acid condition of the stomach is proved by the results of this series of experiments. In five animals sodium bicarbonate, in large doses, was administered by a stomach-tube every few hours from the time the last adrenal was removed until death occurred. While it is impossible to state that alkaline reaction of the stomach-contents was maintained, it is certain that very little acid reached the duodenum. At necropsy in these animals the pancreas presented the same characteristic appearance as in other adrenalectomized animals.

Experiment 5 (Series G).—Dog B169. February 12, 1915, right adrenal removed. February 22, 1915, at 10.45 A. M., the left gland was removed. Sodium bicarbonate in 5 gm. doses was administered about every four hours until death on February 28, 1915, at 8 A. M.

Necropsy.—Pancreas very dark, mulberry color; blood-vessels markedly injected.

Series H.—In six experiments, after removing one adrenal the pancreatic ducts were doubly ligated and sectioned. At different times, varying from a few days to a few weeks, the remaining adrenal was removed. At autopsy of these animals the pancreas did not show the characteristic color and injected blood-vessels. In the experiments in which the last adrenal was removed shortly after ligation of the ducts the pancreas appeared normal; when a few weeks had elapsed between operations, the gland was converted into a hard, fibrous mass. The following experiment is an example:

Experiment 5 (Series H).—Dog B83. Small terrier, about eight months old. November 10, 1914, at 11 A. M., both pancreatic ducts were ligated and right adrenal removed. At 4 P. M. seemed to have recovered from anesthetic and immediate effects of operation.

November 11, 1915: Remaining adrenal was removed.

November 12, 1915: Animal appeared normal.

November 13, 1915: Developed the signs of adrenal insufficiency and died at 2 P. M.

Necropsy.—Site of the operations in good condition. Pancreas normal color, lobules stand out prominently; vessels not injected; firm; duct ligatures holding.

In one series of five experiments after the removal of both adrenals and the development of the moribund condition of adrenal insufficiency, the animals were bled to death. At necropsy the blood-vessels of the pancreas were found to be still markedly injected with blood.

METHOD B.—HISTOLOGIC CHANGES IN THE PANCREAS AFTER ADRENALECTOMY

Sections of the pancreas removed at necropsy from doubly adrenalectomized animals, when stained by the common methods, were rather characteristic. The islands were prominent, engorged with blood, and seemed more numerous than in sections from normal animals. The acinar tissue seemed to be decreased in amount. In order to study these changes to better advantage, the special differential stains of Bensley⁶ were used. After the careful

study of many sections from different animals, the following facts were ascertained:

1. There is a marked congestion which appears to be hypostatic in character. Every capillary seems filled with blood.

2. There is very little or no zymogen present. When zymogen is present, it is found in the acinar cells which surround the islands or the small blood-vessels. This loss of zymogen seems proportionate to the length of time that the animal has been moribund, the greatest loss being found in those cases in which the specimens were secured an hour or so after death. If the gland was removed immediately after death, there was less zymogen than if the animal was bled to death a few hours before it would otherwise have died. This loss of zymogen seems to be more closely related to the decrease in blood-pressure than to the rate of pancreatic secretion. Evidently the storage function of the acinar cells was affected more by the decreased food supply than by secretion.

3. The islands appear larger and more numerous than in sections from the normal animal. On close examination, after using Bensley's stains, some of these apparent islands were found to consist partially of island cells and partially of degenerated acinar cells. Some apparent islands were made up entirely of degenerated acinar cells.

4. The number and size of the islands, as well as the zymogen content, seem to depend on the length of time that the animal is moribund as well as on the length of time after death that the tissue is removed and fixed. Degenerative changes in the pancreas apparently occur slowly during the dying state and very quickly after death. The acinar cells show these changes before they appear in the island cells. The former lose their shape with the loss of zymogen, becoming more rectangular. The nucleus seems to move into the center of the cell. Both nucleus and cytoplasm stain much less intensely. Degeneration granules which take the acid stain appear in the protoplasm. All these changes make the acinar cells appear more like the island cells. As the changes proceed these groups of degenerated cells coalesce and a line of demarcation appears around them. The acini nearest the true islands

seem most affected. They apparently join with the group of island cells to form a larger island. Isolated groups of these changed acinar cells increase the number of the apparent islands.

SUMMARY

The following facts may be taken to express a specific relationship between the adrenals and the pancreas:

1. The pancreas develops a characteristic pink color, and its blood-vessels are injected to a maximum degree after double adrenalectomy. This appearance is not dependent on the acid condition of the fluid in the stomach, but is probably associated with patent pancreatic ducts. The blood found in the injected pancreatic vessels cannot be removed by a free hemorrhage.
2. In an anesthetized animal the flow of pancreatic juice is always slightly increased after the removal of the adrenals.
3. There is a marked decrease in the zymogen content of the pancreas in adrenalectomized animals.

Against these data are the following:

1. The hyperemic condition of the pancreas does not take place until there is evidence that arterial tone is decreasing in the other organs.
2. The increased flow of pancreatic juice in the anesthetized animal after removal of the adrenals is but little greater than that which occurs in the normal anesthetized dog under the same conditions as regards blood-pressure, etc., and it does not exceed the increase incident to the trauma from the removal of only one adrenal. Further, the flow is insignificant as compared to the flow during the process of digestion. In an unanesthetized animal no increase in flow of pancreatic juice after removal of the adrenals is demonstrable.
3. The decrease in zymogen content is proportional to the time of low blood-pressure.
4. All the changes found in the pancreas are proportionate to the length of time that the animal was in a moribund condition.

From a comparison of these data it is seen that all the changes found in the pancreas grossly, histologically, and functionally, after

removal of the adrenals, can be accounted for by the changes in general taking place in the organism as a whole, due to decreased blood-pressure, decreased temperature, and the other changes incident to the development of the moribund condition. We have been unable to demonstrate any specific relationship between the adrenals and the pancreas.

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STUDIES IN THE PATHOLOGY OF THE SPLEEN

II. Pathology of Spleens Removed for Certain Abnormal Conditions of the Blood *

LOUIS B. WILSON

This study is a continuation of a previous report¹ which covered the pathologic examination of 26 spleens removed at operation or autopsy in the Mayo Clinic, between November 14, 1905, and November 1, 1912, from patients on 18 of whom a more or less positive clinical diagnosis of splenic anemia had been made, and of two "wandering spleens" removed at operation within the same period.

The present preliminary report covers the examination of 31 more spleens removed at operation, between December 3, 1912, and June 9, 1915. Further study of the several groups will be reported later. The cases have been studied clinically by Giffin,² whose grouping is observed in the following brief abstracts of the pathologic protocols:

GROUP 1 (15 CASES).—CLINICAL DIAGNOSIS—SPLENIC ANEMIA

CASE I (A76,471).—F. B.; male; aged thirty; duration of symptoms, six months; splenectomy December 3, 1912. Weight of spleen, 1520 gm.; notch distinct; marked perisplenitis over convex surface; capsule thickened; on section, tough, hard, with marked fibrosis. Microscopic examination shows diffuse hypertrophic fibrosis (chronic splenitis); pulp 1†; lymphoid tissue 1; reticulum 4; endothelium of sinuses 1; pigment 3; amyloid degeneration 3; arteriosclerosis 3.

* Read before the American Surgical Association, Rochester, Minn., June 10, 1915. Reprinted from *Annals of Surgery*, 1915, lxii, 157-164.

† The figures 0, 1, 2, 3, 4 indicate relative amounts.

CASE II (A77,560).—M. P.; female; aged twenty-four; duration of symptoms, twelve months; splenectomy December 28, 1912. Weight of spleen, 1770 gm.; notch obliterated; exterior nodular; on gross section, hard, firm, tough. Microscopically, there is diffuse hypertrophic fibrosis (chronic splenitis); pulp 1; lymphoid tissue 1; reticulum 4; endothelium of sinuses 2; pigment 1; amyloid degeneration 3; arteriosclerosis 3.

CASE III (A82,918).—O. N. T.; male; aged thirty-three; duration of symptoms, thirty-six months; splenectomy April 25, 1913. Weight of spleen, 2000 gm.; four notches, one over tip; exterior slightly roughened; no perisplenitis; on gross section, fairly hard and tough; vessels thick-walled. Microscopic sections show diffuse hypertrophic fibrosis (chronic splenitis); pulp 1; lymphoid tissue 2; reticulum 4; endothelium of sinuses 2; pigment 1; amyloid degeneration 1; arteriosclerosis 3.

CASE IV (A48,060).—W. A. C.; male; aged thirty-four; duration of symptoms, twelve months; splenectomy April 2, 1913. Weight of spleen, 600 gm.; notch distinct, but not marked; surface smooth; slight perisplenitis at hilum; somewhat firm on section. Microscopically, there is diffuse fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 3; endothelium of sinuses 3; pigment 1; amyloid degeneration 3; arteriosclerosis 1.

CASE V (A89,075).—N. B. S.; male; aged thirty-five; duration of symptoms, six (?) months; splenectomy October 10, 1913. Weight of spleen, 1030 gm.; broad, flat, with well-marked notch; surface slightly nodular; considerable perisplenitis; capsule thickened; on section, fairly hard and tough; amyloid changes showing grossly (sago spleen). Microscopically, there is diffuse hypertrophic fibrosis (chronic splenitis); pulp 2, edematous; lymphoid tissue 2, edematous; reticulum 3; endothelium of sinuses 3, edematous; pigment none; amyloid degeneration 3; arteriosclerosis 2.

CASE VI (A99,539).—A. F. D.; male; aged forty-five; duration of symptoms, forty-eight months; splenectomy February 3, 1914. Weight of spleen, 680 gm.; thin, flat; marked double notch; considerable perisplenitis; capsule thickened; cuts rather easily; gross subcapsular amyloid changes. Microscopic sections show diffuse fibrosis (chronic splenitis); pulp 1; lymphoid tissue 1; reticulum 3; endothelium of sinuses 3; pigment none; amyloid degeneration 2; arteriosclerosis 1.

CASE VII (A109,051).—S. F. R.; female; aged forty-five; duration of symptoms, sixty months; splenectomy July 9, 1914. Weight of spleen, 560 gm.; very slight notch; gland normal in shape; exterior slightly nodular; very little perisplenitis; capsule not thickened; cuts readily; slightly harder than normal. Microscopic sections show diffuse fibrosis (chronic splenitis); pulp 1; lymphoid tissue 2; reticulum 3; endothelium of sinuses 3; pigment none; amyloid changes 1; arteriosclerosis 1.

CASE VIII (A118,388).—C. H. B.; male; aged twenty-four; duration of symptoms, thirty-six months; splenectomy November 24, 1914. Weight of spleen, 900 gm.; normal symmetry; very slight notch; surface nodular; slight perisplenitis; capsule not thickened; on gross section, hard, firm, tough; marked amyloid (sago spleen); vessel-walls grossly thickened. Microscopically, there is diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 3; endothelium of sinuses 2; pigment 0; amyloid degeneration 4; arteriosclerosis 2.

CASE IX (A118,619).—S. T.; male; aged sixteen; duration of symptoms, sixty months; splenectomy November 26, 1914. Weight of spleen, 875 gm.; elongated; marked notch on each margin; marked perisplenitis; capsule thickened; considerable subcapsular pigmentation in some areas; firm and hard on section. Microscopically, there is a diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 4; endothelium of sinuses 2; pigment 2; amyloid degeneration 1; arteriosclerosis 2.

CASE X (A119,565).—A. M.; female; aged sixty-one; duration of symptoms, twelve (?) months; splenectomy December 9, 1914. Weight of spleen, 500 gm.; elongated; deep single notch; slight perisplenitis; exterior slightly nodular; cuts readily; only slight increase in density. Microscopic sections show diffuse fibrosis (chronic splenitis); pulp 1; lymphoid tissue 2; reticulum 2; endothelium of sinuses 3; pigment 0; amyloid degeneration 1; arteriosclerosis 0.

CASE XI (A115,696).—H. F.; female; aged forty-four; duration of symptoms, one hundred and twenty months; splenectomy October 21, 1914. Weight of spleen, 830 gm.; elongated; multiple notches on both edges; surface roughly nodular; on gross section, cuts with some increased resistance; one large infarct; considerable amyloid degeneration. Microscopically, there is diffuse hypertrophic fibrosis (chronic splenitis); pulp 1; lymphoid

tissue 2; reticulum 3; endothelium of sinuses 2; pigment 0; amyloid degeneration 2; arteriosclerosis 3.

CASE XII (A121,871).—H. E.; male; aged fifty-four; duration of symptoms, eight months; splenectomy January 13, 1915. Weight of spleen, 950 gm.; surface smooth; slight perisplenitis; capsule not thickened; on gross section, fairly firm; slight fibrosis. Microscopic examination shows a diffuse hypertrophic fibrosis of moderate degree (early chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 2; endothelium of sinuses 2; pigment 0; amyloid degeneration 0; arteriosclerosis 2.

CASE XIII (A77,736).—C. B.; male; aged twenty-six; duration of symptoms, twelve months; splenectomy January 13, 1913. Weight of spleen, 2290 gm.; gland broad; one small notch; surface nodular; marked perisplenitis; capsule markedly thickened; considerable amyloid (sago spleen); hemorrhages in several areas with pigmentation. Microscopic examination shows marked diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 1; reticulum 4; endothelium of sinuses 1; pigment 2; amyloid degeneration 3; arteriosclerosis 3.

CASE XIV (A64,405).—M. R. C.; female; aged twenty-eight; duration of symptoms, thirty-six months; splenectomy April 9, 1913. Weight of spleen, 1346 gm.; thick, with small notch; external surface slightly roughened; considerable perisplenitis; capsule slightly thickened; one large infarct; amyloid degeneration (sago spleen). Microscopic examination shows diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 3; endothelium of sinuses 1; pigment 1; amyloid degeneration 2; arteriosclerosis 0.

CASE XV (A132,194).—T. K.; female; aged fifty-one; duration of symptoms, twenty-four months; splenectomy June 9, 1915. Weight of spleen, 1200 gm.; normal symmetry with marked notches both borders; surface markedly nodular; very little perisplenitis; gross section shows subcapsular amyloid degeneration. Microscopically, there is diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; endothelium of sinuses 2; pigment 0; amyloid degeneration 2; arteriosclerosis 1.

SUMMARY OF PROTOCOLS OF GROUP I—SPLENIC ANEMIA

It will be seen from the above protocols that the average age of the patients with a blood-picture of splenic anemia at the time

of operation was thirty-six years. The average duration of symptoms was thirty-two months. The average weight of the spleen was 1130 gm. This is a little higher than the average weight (1040 gm.) of the spleens from our positive splenic anemia (revised clinical classification) cases reported in 1913. The average of the two groups is 1093 gm. Few of the specimens equal the weights given by Lyon,³ who states that the average weight is 62 ounces (1860 gm.). This discrepancy is probably due to the fact that Lyon's figures are drawn largely from autopsy reports, while ours are from operative material, the spleen continuing to enlarge until death. In general the change in the shape of the spleen is not so marked as the change in size. In other words, the hypertrophy is evenly diffuse except in those cases in which infarcts have occurred. The maintenance of the notch is important from the standpoint of clinical diagnosis.

Histologically, the most constant features are the marked reduction of the pulp and lymphoid tissue, with the great increase of reticulum and the almost constant presence of amyloid degeneration and arteriosclerosis. Whether the diffuse hypertrophic fibrosis is the result of inflammatory changes has not been accurately determined. I see no reason at present, however, to change from the commonly accepted theory that the process is one of low-grade chronic inflammation. In this connection it may be noted that Bunting has isolated a diphtheroid organism in pure culture in 4 out of 12 tubes shown from the spleen in our Case XII.

GROUP 2 (7 CASES).—CLINICAL DIAGNOSIS—ACQUIRED PER- NICIOUS ANEMIA

CASE I (A98,774).—M. S.; female; aged fifty-four; duration of symptoms, three months; splenectomy December 11, 1914. Weight of spleen, 360 gm.; normal in contour, with well-marked notch; external surface slightly nodular; no perisplenitis; on gross section, cuts freely, firm but not tough. Microscopically, there is a well-marked lymphocytosis with a slight fibrosis; pulp 3; lymphoid tissue 3; reticulum 2; endothelium of sinuses 2, atrophic; pigment 1; amyloid 0; arteriosclerosis 0.

CASE II (A112,160).—D. Mc.; female; aged fifty-five; duration of symptoms, twenty-four months; splenectomy August 11, 1914. Weight of spleen, 300 gm.; general contour fairly normal; small notch on each border with deep groove connecting the two; surface slightly nodular; no perisplenitis; on section, capsule not thickened; cuts readily, though firm. Microscopic examination shows a marked lymphocytosis with a slight fibrosis; pulp 2; lymphoid tissue 4; reticulum 2; endothelium of sinuses 2, atrophic; pigment 0; amyloid degeneration 0; arteriosclerosis 0.

CASE III (A112,836).—D. D. B.; female; aged forty-eight; duration of symptoms, thirty-six (?) months; splenectomy August 27, 1913. Weight of spleen, 910 gm.; short, broad, thick, notch almost obliterated; surface slightly roughened; on gross section, the gland is firm, hard, tough, and very dark colored. Microscopically, there is a diffuse hypertrophic fibrosis (chronic splenitis); pulp 2; lymphoid tissue 2; reticulum 3; endothelium of sinuses 2, atrophic; pigment 0; amyloid degeneration 1; arteriosclerosis 1.

CASE IV (A124,257).—M. S.; male; aged twenty-six; duration of symptoms, twelve months; splenectomy March 10, 1915. Weight of spleen, 500 gm.; fairly normal contour, with well-marked notch; external surface smooth; no perisplenitis; on section, organ is hard though not tough. Microscopically, there is a marked lymphocytosis and moderate fibrosis; pulp 2; lymphoid tissue 4; reticulum 2; endothelium of sinuses 2, atrophic; pigment absent; amyloid degeneration 1; arteriosclerosis 0.

CASE V (A127,677).—C. H.; male; aged thirty-five; duration of symptoms, three (?) months; splenectomy April 17, 1915. Weight of spleen, 186 gm.; fairly normal in contour; very slight notch; on gross section, fairly firm but not tough. Microscopically, there is a marked lymphocytosis with atrophic fibrosis; pulp 1; lymphoid tissue 4; reticulum 1; endothelium of sinuses 2, atrophic; pigment 0; amyloid degeneration 0; arteriosclerosis 0.

CASE VI (A129,678).—D. D. B.; female; aged forty-eight; duration of symptoms, one hundred and eight months; splenectomy June 4, 1915. Weight of spleen, 486 gm.; general contour thickened; external surface slightly nodular; slight perisplenitis; on gross section, capsule not thickened; organ cuts readily, though firmly, no fibrosis. Microscopically, there is a marked lymphocytosis with a slight fibrosis; pulp 2; lymphoid tissue 4;

reticulum 2; endothelium of sinuses 2, atrophic; pigment 0; amyloid degeneration 0; arteriosclerosis 0.

CASE VII (A128,367).—J. H. D.; female; aged forty-one; duration of symptoms, three months; splenectomy June 5, 1915. Weight of spleen, 500 gm.; in contour, broad and thick, with very slight notch; external surface smooth; no perisplenitis; on section, organ is firm, but not tough. Microscopically, there is a marked lymphocytosis with a moderate fibrosis; pulp 2; lymphoid tissue 3; reticulum 2; endothelium of sinuses 2; pigment absent; amyloid degeneration absent; arteriosclerosis absent.

SUMMARY OF PROTOCOLS OF GROUP 2—ACQUIRED PERNICIOUS ANEMIA

The average age of patients with pernicious anemia was forty-four years at the time of operation. The average duration of symptoms was twenty-seven months. The average weight of the spleens removed was 463 gm. Only one was less than normal (195 gm.).⁴ The increase in weight is out of harmony with our conception of the atrophy usually found in the spleen in cases of pernicious anemia.⁵ Here again the discrepancy is probably accounted for by the fact that in the last stages of pernicious anemia the spleen becomes atrophic, while our figures, based on operative cases, show an increased weight of the organ.

Cytologically, the increase is mostly in the lymphoid tissue, though it is worthy of note that in one case (Case III) there was a well-marked fibrosis, this spleen weighing almost twice the average weight of the glands in the series. The almost entire absence of pigment in these relatively early stage cases is again in contradiction to the usually accepted statement that in cases of pernicious anemia the spleen is pigmented.

GROUP 3 (1 CASE).—CLINICAL DIAGNOSIS—HEMOLYTIC ANEMIA

CASE I (A122,468).—J. B. McG.; male; aged sixty-four; duration of symptoms, fifteen months; splenectomy January 23, 1915. Weight of spleen, 1120 gm.; organ very thick, with well-marked notch; external surface roughened; marked perisplenitis; on section, capsule is not thickened; organ is hard and firm, but not

tough; very pale; little amyloid. Microscopically, there is a diffuse hypertrophic fibrosis with lymphocytosis (chronic splenitis); pulp 2, lymphoid tissue 3; reticulum 3; endothelium of sinuses 2, swollen; no pigment; amyloid degeneration 2; considerable hemorrhage.

GROUP 4 (1 CASE).—CLINICAL DIAGNOSIS—SECONDARY INFECTIOUS OR SEPTIC SPLENOMEGALY

CASE 1 (A107,092).—J. P. H.; male; aged thirty-one; duration of symptoms, three months; splenectomy June 27, 1914. Weight of spleen, 700 gm.; organ swollen; no notch; marked perisplenitis; on section, gland is fairly firm, though soft and not tough; several small infarcts. Microscopically, there is a sub-acute splenitis; pulp 2, necrotic; lymphoid tissue 3, swollen; reticulum 2; endothelium of sinuses 2, atrophic; pigment absent; amyloid degeneration absent; no arteriosclerosis.

GROUP 5 (2 CASES).—CLINICAL DIAGNOSIS—SYPHILIS WITH SPLENOMEGALY

CASE 1 (A119,102).—G. H. I.; female; aged forty; duration of symptoms, twenty-four months; splenectomy December 4, 1914. Weight of spleen, 900 gm.; gland normal in contour, with very marked notch and dorsal groove; external surface slightly nodular; considerable perisplenitis; on section, organ is firm, tough, and very dark colored. Microscopically, there is a diffuse fibrosis with a moderate lymphocytosis; pulp 3; lymphoid tissue 3; reticulum 3; endothelium of sinuses 2, atrophic; pigment 1; amyloid degeneration 0; arteriosclerosis 3.

CASE II (A125,899).—H. S. D.; female; aged thirty-two; duration of symptoms, ten (?) months; splenectomy April 1, 1915. Weight of spleen, 670 gm.; gland long and slender; no notch; slightly roughened surface; considerable perisplenitis; on gross section, organ is pale and firm, but not tough. Microscopically, there is a moderate diffuse fibrosis; pulp 2; lymphoid tissue 2; reticulum 3; endothelium of sinuses 2, swollen; pigment 0; amyloid degeneration 0; arteriosclerosis 2.

GROUP 6 (2 CASES).—CLINICAL DIAGNOSIS—HEMOLYTIC JAUNDICE

CASE I (A41,779).—J. T. G.; female; aged fifty-one; duration of symptoms, forty-two months; splenectomy October 28, 1913.

Weight of spleen, 640 gm.; gland broad, thick, with well-marked notch on each border; surface rough; considerable perisplenitis; on section, organ is pale, firm, and hard. Microscopically, there is a moderate hypertrophic fibrosis; pulp 1; lymphoid tissue 2; reticulum 3; endothelium of sinuses 2; pigment 1; amyloid degeneration 0; arteriosclerosis 1.

CASE II (A86,218).—A. J. H.; aged thirty-three; duration of symptoms, eighteen months; splenectomy June 30, 1913. Weight of spleen, 900 gm.; elongated; very slight notch; external surface nodular; considerable perisplenitis; on gross section, organ firm, hard, but not tough. Microscopically, there is a hypertrophic fibrosis (chronic splenitis); pulp 2, swollen; lymphoid tissue 3, swollen; reticulum 3; endothelium of sinuses 2; pigment 0; amyloid degeneration 0; arteriosclerosis 1.

GROUP 7 (1 CASE).—CLINICAL DIAGNOSIS—LYMPHOSARCOMA

CASE I (A108,557).—C. V.; male; aged forty-five; duration of symptoms, two months; splenectomy July 3, 1914. Weight of spleen, 1870 gm.; very broad and thick; very deep notch on border; surface rough and scarred by infarcts; on section organ is soft and dark. Microscopically, there is a diffuse lymphosarcoma; pulp 4; lymphoid tissue 4; reticulum 1; endothelium of sinuses 1, atrophic; pigment 0; amyloid degeneration 0.

GROUP 8 (1 CASE).—CLINICAL DIAGNOSIS—ACUTE FEBRILE
NON-SEPTIC (?) SPLENOMEGALY

CASE I (A117,048).—L. J. L.; male; aged thirty; duration of symptoms, one (?) month; splenectomy October 27, 1914. Weight of spleen, 1940 gm.; gland swollen; slight notch; external surface smooth; some perisplenitis; on gross section, organ is soft and dark colored. Microscopically, there is a parenchymatous hyperplasia; pulp 3; lymphoid tissue 3; reticulum 1; endothelium of sinuses 3, swollen; pigment 0; amyloid degeneration 0; arteriosclerosis 0.

GROUP 9 (1 CASE).—CLINICAL DIAGNOSIS—SPLENOMEGALY WITH
EOSINOPHILIA

CASE I (A81,201).—F. H.; male; aged thirty-one; duration of symptoms, twelve months; splenectomy July 15, 1914. Weight of spleen, 2110 gm.; organ very thick, broad; well-marked notch; external surface rough; very marked perisplenitis; on section,

gland is very soft. Microscopically, there is a marked parenchymatous hyperplasia; pulp 4; lymphoid tissue 2; reticulum 1; endothelium of sinuses 2, swollen; pigment 3; amyloid degeneration 0; many eosinophiles throughout splenic tissue.

GENERAL SUMMARY OF THE LAST SEVEN GROUPS

The cases of hemolytic anemia, lues, and hemolytic jaundice resemble pathologically the cases of splenic anemia. The cases of secondary infection, lymphosarcoma, acute febrile non-septic splenomegaly, and splenomegaly with eosinophilia have little pathologic relationship to either splenic anemia or pernicious anemia. The lymphosarcoma case is a typical lymphoma whose malignancy was shown clinically. The other three cases give the general picture of an intense acute or subacute infection, causing hypertrophy and hyperplasia of all the parenchymal elements of the spleen without material increase in the reticulum.

Our knowledge of the pathology of splenomegaly associated with chronic changes in the blood has made slow progress, largely because—except in rare instances—we have been unable to study spleens from such cases until the later or terminal stage of the diseases has been reached. Now that splenectomies are becoming more common, it is fair to assume that clinicians will be on the lookout for large spleens in all cases of pathologic conditions of the blood, and that we may hope for opportunity to study early pathologic changes in the glands removed at operation. If any progress is to be made, however, we must sharply differentiate the relative changes in the various histologic elements of the spleen, and these changes must be studied in correlation with accurately observed clinical phenomena. At present the clinical diagnoses of splenic anemia, pernicious anemia, secondary infectious anemia, hemolytic jaundice, Gaucher's disease, etc., are all lacking in clearness, a condition which must be materially improved upon before an instructive parallel may be shown—if, indeed, any exist—between the several clinical syndromes in their various stages and the pathologic picture present in the spleen.

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DISEASES OF THE SPLEEN

III. Clinical Notes on Splenectomy *

HERBERT Z. GIFFIN

In June, 1913, I published a detailed report of the clinical observations in 27 cases of splenectomy. At the present time it is my purpose to review, not in detail, but only in a general way, the clinical characteristics of the 58 cases of splenectomy in the Mayo Clinic since 1904. One of our patients is alive and well eight years after operation. In this instance the history was analogous to that of splenic anemia, while the spleen showed pathologically a lymphocytic hyperplasia, not, however, with any definite evidence of malignancy. The next longest period for which a patient has remained well is seven years. In this instance there was a clinical history similar to that of splenic anemia, while pathologically the spleen showed endothelial proliferation and the case might be said to correspond to the Gaucher type of splenic anemia. One patient has been alive and well for six years, 2 patients have been in good health five years, 2 four years, and 3 three years following operation. Pathologically, the spleens in these latter cases showed a connective-tissue increase with an atrophy of the Malpighian bodies.

Many types of splenomegaly are necessarily represented in this series, and any classification of the cases is, of course, open to discussion and criticism. On the basis of their clinical and pathologic characteristics they will be presented in groups as follows:

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SPLENECTOMY, APRIL 6, 1904-JUNE 9, 1915

Splenic anemia (pathologically diffuse fibrosis) . . .	27 cases
Gaucher's disease (endothelioid hyperplasia)	3 cases *
Pernicious anemia	7 cases
Hemolytic anemia (marked splenomegaly)	2 cases
Secondary infectious or septic splenomegaly	5 cases
Lues (marked splenomegaly)	2 cases
Acquired hemolytic (hematohepatogenous) jaundice	2 cases
Cirrhosis of liver	1 case
Myelocytic leukemia	1 case
Lymphoma or lymphosarcoma	3 cases
Tuberculosis of spleen	1 case
Wandering spleen	2 cases
Acute febrile non-septic (?) splenomegaly	1 case
Splenomegaly with marked eosinophilia	1 case
Total	58 cases

Splenic Anemia.—In this group have been placed the 27 patients in whom the enlargement of the spleen was very great and in whom splenomegaly seemed to be the primary condition. The development of a severe type of anemia with low color index and an absence of leukocytosis were regarded as essential. Hematemesis occurred in a majority of the cases. Pathologically all the spleens showed an increase of connective tissue. There were 3 operative deaths in the group, while the total number of deaths was 8 in ten years. Hemorrhage was the cause of death in 2 instances, in 1 case occurring one year after operation and in the other five and one-half years. In 3 other instances hemorrhage occurred 2 and 3 times at different periods after operation, but the patients are at present in good health. It is evident that the patients in this group had a low operative risk and an excellent prospect of cure.

Gaucher's Disease.—Our 3 cases in which the spleen showed evidence of endothelioid hyperplasia occurred early in the series. We have been unable to obtain a history of familial tendency in any of them. One of these patients is in excellent health seven years following operation. In 2 patients the spleen had probably been enlarged since adolescence.

Pernicious Anemia.—Seven patients with pernicious anemia have been operated since August, 1914, with one operative death.

* Two of these cases have been questioned. A more detailed report will be published later.

A second patient died two months after operation with severe anemia. The third patient, two and one-half months after operation, is in very good health, with hemoglobin at 70 per cent. In the fourth patient the condition of the blood rapidly improved after the operation, and the hemoglobin was 75 per cent. in three months. The fifth patient, nine months after operation, had gained 23 pounds, the hemoglobin was 70 per cent. and the red blood-count 3,026,000. The last two patients are at present in the hospital. It is therefore seen that in our small series of splenectomies for pernicious anemia there was 1 operative death, 1 death at two months, while 3 of the patients showed marked temporary improvement. Many patients with pernicious anemia have presented themselves for diagnosis, but we have hesitated to advise surgical treatment.

Hemolytic Anemia with Very Much Enlarged Spleen.—There were 2 cases of an unusual type in which the anemia was severe in character, but in which the typical count of pernicious anemia was not present and in which the spleen was very much larger than that ordinarily seen in pernicious anemia. The first patient (A7040) was operated on February 10, 1910. The blood count showed a rather high color index, not, however, above 1, and there were a few normoblasts and megaloblasts in the smears. The spleen was very large, weighing 1640 gm. After operation showers of normoblasts occurred, a finding which is quite unusual in other types of splenomegaly save that of pernicious anemia. The second patient (A122,468) was operated on January 23, 1915. The spleen was enlarged early in the history of the disease, apparently before the development of anemia; the blood findings were similar to those of the first patient, and the spleen was large, weighing 1120 gm.

It is true that these two cases may in reality be pernicious anemia, but the great size of the spleen, the fact that at no time was the blood typical of pernicious anemia, and the further observation that the enlargement of the spleen occurred early in the disease, would rather lead to the conclusion either that they belong to a separate group in the production of which a disturbance of splenic function may have been primary, and in which the reaction of the

bone-marrow was different from that in splenic anemia, or that they were instances of a type of pernicious anemia unusually active both with respect to blood production and blood destruction.

Secondary Infectious or Septic Splenomegaly.—Under this heading have been placed five cases in which the enlargement of the spleen was not marked, in which the splenomegaly did not seem to be a primary factor in the production of anemia, and in which there was evidence of preceding abdominal or systemic sepsis. One of these patients was in good health five years following operation.

Lues with Splenomegaly.—There were two instances in which large, non-gummatous spleens together with secondary types of anemia were present in patients with strong positive Wassermann reactions. In one of these the liver was smooth and specific treatment had been given elsewhere without benefit. Splenectomy was followed by marked improvement. In the other instance large palpable gummas were present in the liver. These were very much reduced by specific treatment before operation, but the size of the spleen and the degree of anemia were not affected. In this case improvement has also been marked since splenectomy.

Acquired Hemolytic Jaundice.—Two cases have been classified as hemolytic jaundice. It is possible that both of them may have been instances of biliary cirrhosis of the liver. Chronic jaundice was prominent in these patients and anemia marked.

Cirrhosis of the Liver.—One case has been regarded as cirrhosis of the liver. In this patient neither was the spleen large nor the anemia marked. Advanced portal cirrhosis was found at operation.

Myelocytic Leukemia.—A patient classified in our report of 1913 as a case of splenic anemia, and so regarded by careful observers in other clinics, but of whom it was noted at the time that the blood picture was not entirely satisfactory for this grouping, continued to be in fairly good health for five and one-half years, after which the leukocyte count became increased to 64,000 with 14 per cent. of myelocytes.

Lymphoma or Lymphosarcoma.—Our series includes 2 cases of lymphosarcoma of the spleen. One of the patients remained well

for several years but finally died with generalized malignancy nine years after operation. The second patient was operated on July 3, 1914, at which time there was no evidence of metastases. After operation, however, general glandular enlargement rapidly occurred and death supervened five months later. A third patient presenting a decided lymphocytic hyperplasia pathologically, but no definite evidence of malignancy, is well eight years after operation.

Tuberculosis of the Spleen.—In 1904 a large spleen which proved to be tuberculous was removed from a patient who at the time of operation gave no definite evidence of tuberculosis elsewhere in the body.

Wandering Spleen.—Two cases of this type were operated on because of pain resulting from twisted pedicle. These patients are both alive and well three and seven years following operation.

Acute Febrile Non-septic Splenomegaly.—Several of the cases in this series were very unusual in their clinical manifestations and in the combination of conditions present. One of them was analogous in many ways to those cases occurring in Egypt, and reported as Egyptian splenomegaly, and deserves detailed description.

The patient (A117,048) was a man, aged thirty years, who gave a history in which there was no record of previous disease. He had seemed to be toxic and somewhat stupid for six or eight weeks, while a remittent fever reaching 103° F. had been present. There had been abdominal enlargement for only two weeks, but no history of hematemesis, while ascites was present at the time of examination and the spleen could be felt on ballottement. Wassermann test, Widal reaction, blood cultures, etc., were negative. In spite of the history of fever and the acute course of the disease, there was no leukocytosis, but a definite leukopenia with a relative increase of lymphocytes and an anemia of the secondary type with hemoglobin at 70 per cent. The patient remained under observation for three months, the condition became less acute in character, and splenectomy was finally decided on. The spleen was very large, weighing 1940 gm., and the liver was somewhat cirrhotic. (The patient remained weak after operation, had 3 hemorrhages from the bowels, and finally died five months following operation.) The acute course, the presence of high fever, the rapid develop-

ment of a very large spleen and ascites, the absence of leukocytosis, and other evidence of sepsis, and the absence of jaundice formulate the picture of a most unusual type of splenomegaly.

Splenomegaly with Marked Eosinophilia.—As far as we have been able to determine, there is no case of this type to be found in the literature.

This patient (A81,201) was a man, aged thirty-one years. He was first seen in March, 1913. He had had a continued fever which was diagnosed as typhoid eight years previous, and had complained of weakness since that time. Transitory edema had been present for ten months and had become extreme within ten days. At the time of his first visit there was a general anasarca, on account of which he was placed on milk diet, and the edema disappeared in ten days. The blood count at that time showed a secondary type of anemia, with hemoglobin at 69 per cent. and a leukocyte count of 15,400, while the most remarkable feature was the presence of a 66 per cent. eosinophilia. The patient was under observation for three months, during which time many blood-counts were made and verified by experienced hematologists and the eosinophiles varied from 58 to 77 per cent. Wassermann tests were negative; stools were negative; and the examination of muscle for trichinæ was also negative, although not entirely satisfactory. The great enlargement of the spleen persisted and operation was finally decided on and performed in July, 1914. The spleen weighed 2110 gm. The patient has done well since the operation; his leukocyte count, however, has risen to 138,000, of which from 75 to 80 per cent. are eosinophiles. There is very little basis for speculation as to the possible etiology of this unique case.

RÉSUMÉ

Our series of 58 cases includes 27 of splenic anemia, 3 of the Gaucher type of splenic anemia, 7 of pernicious anemia, 2 of hemolytic jaundice, 5 of secondary infectious or septic splenomegaly, 2 of an unclassified type of hemolytic anemia with marked splenomegaly, 2 of lues, 3 of sarcoma or lymphoma, 2 wandering spleens, and 1 each of myelocytic leukemia, cirrhosis of the liver, and tuberculosis of the spleen. In addition, it includes 1 case of acute febrile non-septic splenomegaly which is analogous in its

clinical course to Egyptian splenomegaly, and 1 case in which splenomegaly was associated with an extremely high eosinophilic count. Splenic anemia is, in our experience, most favorable for surgical treatment. The operative risk is relatively low, and the prospect for a return to normal health excellent. Three of the 7 patients with pernicious anemia have shown temporary improvement up to nine months after splenectomy. Removal of the spleen in non-gummatous splenomegaly associated with syphilis has been attended with excellent results in two instances.

IV. Splenectomy for Splenic Anemia in Childhood and for the Splenic Anemia of Infancy*

HERBERT Z. GIFFIN

It is my purpose to lead, not to confusion, but rather to a distinction and a comparison by discussing in the same paper the adult form of splenic anemia as it occurs in childhood, and the splenic anemia of infancy (*anæmia pseudoleukæmica infantum*). *Anæmia pseudoleukæmica infantum*, or von Jaksch's disease, seems to have no relationship clinically or pathologically to leukemia, and it is agreed by such authorities as Wentworth,¹ Hutchison,² and Ostrowsky³ that this terminology should be discarded and the disease referred to as infantile splenic anemia or the splenic anemia of infancy. The adult form of splenic anemia as it occurs in children and the splenic anemia of infancy have many characteristics in common, as well as certain distinctive differences.

The blood of children, and particularly the blood of infants under two years of age, differs normally from the blood of adults (Shaw⁴). A moderate leukocytosis which is essentially a lymphocytosis is quite constant, and marrow-cells are occasionally observed. A lymphocyte percentage of 40 and 50 in infants under

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two years of age is observed normally, and this normal lymphocytosis is always to be taken into account in the consideration of any case of infantile anemia. It is also generally recognized that the blood of infants reacts differently than the blood of adults to various toxic agents. A lower red-cell count with a consequent higher color index, the occurrence of degenerated red cells, the presence of normoblasts and occasional megaloblasts, and a leukocytosis of 10,000, 15,000, or 20,000, with the occurrence of eosinophiles and myelocytes, are frequently present in the anemias of infancy.

The splenic anemias of childhood and infancy have been divided by Hunter,³ chiefly according to the blood-picture, into three types. *Type one* corresponds to the clinical picture of the splenic anemia of adults. There is a large spleen, a gradually developing or recurring anemia, and the blood presents the picture of a secondary type of anemia with a relatively low color index and an absence of leukocytosis. Lymphocytes are present in a normal percentage, 40 or 50 per cent., and there is only an occasional normoblast to be found. Hunter's *type two* includes cases in which the leukocyte count is between 10,000 and 20,000, and in which a variable number of normoblasts and megaloblasts are present in the smears. The color index is relatively higher. *Type three* embraces those cases in which the leukocyte count is above 20,000, and great numbers of normoblasts, together with occasional megaloblasts, eosinophiles, and myelocytes occur. Authorities seem to agree that there is no essential distinction between types two and three, and it would apparently be best to classify the cases into two groups: First, those conforming to the syndrome of the splenic anemia of adults, with absence of leukocytosis, and, second, those conforming to that of the splenic anemia of infancy and showing a leukocytosis, the presence of a variable number of marrow-cells, and a relatively high color index.

1. *Splenectomy for the Adult Form of Splenic Anemia in Childhood*.—Reports of cases conforming from a clinical standpoint to the adult form of splenic anemia and Banti's disease in childhood are not uncommon in literature. Reports of cases of this type in

which splenectomy has been done are, however, much less numerous. This discussion will be confined to patients of the first decade.

Gaucher's disease, lymphosarcoma, septic splenomegaly, particularly as associated with endocarditis, and the splenomegalies of syphilis, rickets, and hemolytic jaundice are to be especially excluded in the differential diagnosis of splenic anemia in childhood. I have been able to collect from the literature five cases in which splenectomy has been done for conditions which conform, some of them imperfectly, to the adult type of splenic anemia occurring in children under ten years of age. It is to be regretted that complete pathologic descriptions of the spleen cannot be obtained in all these cases, as the diagnosis is undoubtedly questionable in some of them. Brief descriptions of the collected cases are reviewed, and one case of our own is discussed in detail.

Bland-Sutton,⁶ in 1895, performed a splenectomy on a girl aged five years, with an enlarged spleen and anemia. There was a negative family history and "leukemia, syphilis, rickets, and lardaceous disease were excluded." The spleen weighed 10 ounces. Blood count and pathologic description were not given. Eighteen years later this patient seemed to be a perfectly healthy woman.

Luce¹⁰ reported a splenectomy (November 16, 1908) upon a girl aged six years. The case was very carefully studied, and conformed quite closely to the syndrome of splenic anemia. There was no history of syphilis and no familial tendency. The spleen extended 5 cm. below the costal margin, and a blood count showed: Hemoglobin, 30 per cent., red-cell count, 2,100,000, and leukocyte count, 6700. There was considerable evidence of blood destruction, with an occasional normoblast in the smears. The spleen weighed 240 gm.; there was a hypertrophy of the follicles, a relative atrophy of the lymphatic elements, and marked engorgement of the sinuses. Nine months after operation the patient was in excellent condition.

Sutherland and Burghard⁷ reported splenectomy (1910) in a girl aged six years, in whom the hemoglobin was 30 per cent., the red-cell count 1,870,000, and the white count 2400. A very faint jaundice was present. Two months after operation the hemoglobin was 65 per cent. The spleen showed a generalized hyperplasia and weighed one pound. This case was reported as a

splenic anemia, but is referred to by Elliott and Kanavel⁸ as a doubtful case of hemolytic jaundice.

D'Espine⁹ in 1913 reported a splenectomy in a case which he classified as Banti's disease in a sixteen-months-old girl baby. The spleen weighed 201 gm. and showed a diffuse fibrosis. The anemia was of the secondary type, with a leukocytosis of 16,120, and the presence of an occasional normoblast. The child died six weeks later, and at autopsy a glandular tuberculosis was found, but animal inoculation with splenic tissue gave negative results. D'Espine states that Banti's disease of adults probably dates from early childhood in many cases.

Barling¹¹ reported a splenectomy (February 25, 1914) in a girl aged six years, who had vomited blood ten weeks previously. The spleen extended three inches below the costal margin. The hemoglobin was 60 per cent., red-cell count 3,600,000, and the white varied from 7000 to 26,000. This case cannot be accurately classified because of the fact that the differential count and pathologic description of the spleen were not given. Death occurred on the fourth day after operation, and at autopsy an acute hepatitis was found. Barling also mentions a splenectomy in a boy aged six, by French and Turner,¹² but this case would better be grouped with the splenomegalies associated with syphilis.

In our series of 68 splenectomies for various conditions (September 1, 1915) there has been only one in a patient of the first decade, and this one but a recent case. It will be seen that this case, of which a description follows, corresponds quite accurately from a clinical standpoint to the splenic anemia of adults.

CASE A137,566.—F. M. D., a girl two and one-half years of age, was first examined August 3, 1915. The family history was entirely negative, and anemia, hemophilia, and splenomegaly were inquired about particularly. There were four other children in the immediate family, all healthy, and the mother had had no miscarriages. The patient had evidently been entirely well until about one month before examination, when suddenly she vomited a large quantity of blood, estimated by the parents at one quart, and the stools became black for two or three days. Strength and color were promptly regained, and the patient was soon quite well again. Two weeks before examination a second hemorrhage occurred, less severe than the first. After this second hemorrhage,

however, the patient seemed to get progressively paler and weaker. An abdominal mass was found two weeks before examination. Ten days before examination an eruption which seemed to be urticarial in character appeared and disappeared again in twenty-four hours. There was slight fever at this time, but a history of fever at any other time could not be elicited. The appetite was poor, the bowels were regular, and micturition was normal.

On examination the child was found to be thin and very pale. The abdominal mass could be easily identified by its contour and notch as spleen. It extended to a point below the level of the navel. The liver dulness did not seem to be abnormal. The superficial glands were very slightly enlarged. There was no fever. Wassermann test and Widal reaction were negative. The blood count showed a secondary type of anemia with a color index of 0.4 and an absence of leukocytosis. The hemoglobin was 20 per cent.; a red-cell count was 2,010,000. The red cells showed marked anisocytosis and moderate polychromatophilia, and only one normoblast was seen while counting 300 white cells. There was no increase in the fragility of the red cells. The leukocyte count was 4000. A differential count of 300 cells showed polynuclear neutrophils, 22.7 per cent.; small lymphocytes, 50 per cent.; large lymphocytes, 12.32 per cent.; eosinophiles, 12.3 per cent.; basophiles, 2.3 per cent.; neutrophilic myelocytes, 0.3 per cent.

Operation (D. C. Balfour, August 15, 1915).—Splenectomy in this case did not offer any marked technical difficulties, although the risk was apparently considerable on account of the patient's age and the severe degree of anemia. A left rectus incision was made. The diaphragmatic adhesions rendered dislocation of the spleen somewhat hazardous. A long pack was interposed between the spleen and the oozing diaphragmatic surface to control the bleeding, if possible, without the necessity for suturing later. The edematous condition of the tissues made them very friable, and the pedicle had to be ligated with especial care. It was thought advisable to leave the hemostatic pack in place until the incision had almost closed, and this proved efficacious. The patient's recovery from the operation was surprisingly good; there were no complications, and she left the hospital on the ninth day.

Pathologic Report (L. B. Wilson).—Case A137,566, F. M. D. Weight of spleen, 110 gm.; slight notch; moderate perisplenitis over convex surface; capsule not thickened; on section, gland somewhat tough, showing considerable fibrosis; lymphoid areas

well defined and increased in size. Microscopic examination shows moderate diffuse fibrosis (chronic splenitis); pulp 2; lymphoid tissue 3; reticulum 2; endothelium of sinuses 2; pigment 0; amyloid degeneration 0; arteriosclerosis 1.* It will thus be seen that the most marked changes were the increase in lymphoid tissues (non-diffuse) and stroma and the hypertrophy of the reticulo-endothelium of the sinuses. The arteriosclerosis, though small in amount, is, of course, unusual when the age of the patient is considered.

Subsequent Condition.—Three days following operation the hemoglobin was 27 per cent., the leukocytes had increased to 14,600, of which 71.3 per cent. were polynuclear neutrophils, and 76 normoblasts were seen while counting 300 white cells. Future reports will contain the ultimate result in this case.

2. *Splenectomy for the Splenic Anemia of Infancy.*—The splenic anemia of infancy as a clinical entity was described by Gretscl¹³ in 1866. To this syndrome he gave the name of "splenic anemia of infants." Somma,¹⁴ in 1884, described the same condition under the title of "anæmia splenica infantile." Von Jaksch,¹⁵ in 1888 and 1890, brought the disease more clearly to the notice of the medical profession under the name of "anæmia pseudoleukæmica infantum." Many cases of the splenic anemia of infancy have been reported in the literature, and much discussion has resulted, particularly concerning its relationship to rickets, syphilis, and the gastro-intestinal disturbances. It seems to have been clearly shown that, for the present, at least, it is useful to regard certain cases of severe secondary anemia in infancy with marked splenomegaly and a more or less characteristic blood-picture as a separate disease entity, in spite of the frequent association of rickets.

Splenectomy for the splenic anemia of infancy has been performed, as far as I have been able to find, in but four unquestioned cases.

Wolff,¹⁶ in 1906, operated on a boy baby aged eighteen months, of whom there was a six months' history of illness. The spleen was very large, the blood showed a hemoglobin of 40 per cent., a

*The numbers, 0, 1, 2, 3, 4, indicate the relative amounts of the several tissue elements.

red-cell count of 467,000, and a white-cell count of 37,800. The differential count showed a lymphocytosis and the presence of mast-cells and eosinophiles. There was a considerable poikilocytosis and anisocytosis, and many normoblasts and megaloblasts were present. The child was in very poor condition. Ascites was present, the liver was enlarged, and an operation was advised as a last resort. Splenectomy was performed July 29, 1905. The spleen weighed 500 gm. and showed an induration of the connective-tissue framework, but no enlargement of the Malpighian bodies. There was no increase of lymphocytes in the spleen pulp. By the tenth day after operation the hemoglobin had risen from 40 to 51 per cent., and the red-cell count from 467,000 to 2,500,000, while the leukocytes were 36,000. Three years after operation this patient was presented before the Deutsche Gesellschaft für Chirurgie in excellent general condition. The blood-picture was normal save that the leukocytes had remained increased.

Graff,¹⁷ in 1908, reported the case of a fifteen-months-old baby on whom splenectomy had been done in the summer of 1907. The family history was negative; the child had apparently been normal to the tenth month. After this time the appetite failed and the child lost weight, while there was a gradual increase in the size of the abdomen. At the time of the examination the patient was emaciated, scrawny, yellowish-white in color, and weighed only 11 pounds. There was evidence of mild rickets. The spleen extended beyond the midline and downward almost to the symphysis. The liver did not seem to be enlarged. The blood-count showed a hemoglobin of 45 per cent., a red-cell count of 1,800,000, with many normoblasts and a few megaloblasts. The white-cell count was 37,000, and an examination of the smears showed a lymphocytosis. The spleen measured 16 x 10 x 8 cm., and weighed one pound or nearly one-tenth of the body weight. It was very firm and hard. On examination it showed an increase of connective tissue, occasional hemorrhages, and small collections of lymphocytes, and giant-cell-like structures similar to bone-marrow giant-cells. There was no evidence of tuberculosis or tumor. After splenectomy the patient began immediately to improve. In five weeks the hemoglobin was 50 per cent. and the red-cell count had risen from 1,800,000 to 5,000,000. In nine months the patient was quite well, weighed 21 pounds, and the blood was almost normal.

Fowler¹⁸ performed a splenectomy in April, 1914, on a fourteen-months-old girl baby, in whom the spleen was much enlarged,

the liver was apparently normal and the blood count showed a hemoglobin of 50 per cent., a red-cell count of 3,316,000, giving a color index of 0.9 per cent., with many normoblasts and occasional megaloblasts in the blood smears, together with a considerable variation in the size and the staining qualities of the red cells. The leukocyte count was 30,000, with polynuclears of 40 per cent., large mononuclears 12 per cent., and small mononuclears 38 per cent. One month after operation the hemoglobin was 65 per cent. and the red-cell count 3,430,000, with occasional normoblasts and megaloblasts, the leukocyte count 15,000, of which the small mononuclears was 78 per cent.

Pool¹⁹ performed a splenectomy on a boy baby of nine months on August 17, 1914, after a preliminary blood transfusion of 150 c.c. The infant had been born at seven months, and nutritional disturbances had been troublesome. The child was very poorly developed, anemic, and showed evidence of rickets. The liver extended 2 cm. below the edge of the ribs, and the spleen 5 cm. below the left costal margin. A Wassermann test was negative. The patient had been on preliminary medical treatment for six weeks without improvement. The hemoglobin before operation varied from 30 to 45 per cent., the red count from 1,400,000 to 2,400,000, and the leukocytes from 17,000 to 54,000. A differential count showed polynuclears of 35 per cent., eosinophiles 2 per cent., lymphocytes 49 per cent., transitionals 3 per cent., large mononuclears 6 per cent., and myelocytes 5 per cent. Normoblasts had varied from 6 to 66 per 100 white cells, and of these two or three were megaloblasts. Two months after operation the hemoglobin had risen to 85 per cent., the red-cell count to 4,200,000, and the white-cell count had decreased to 13,300. The high lymphocyte percentage persisted, but the normoblasts were decreased in number. Three months after operation the patient was reported to be not as well as he had been at two months.

None of our cases of the splenic anemia of infancy has so far been operated on, and my purpose in collecting these 4 instances of splenectomy for the splenic anemia of infancy is to call attention to the fact that excellent results have been obtained in very severe types of the disease. Wolff's patient was in excellent condition three years after operation, Graff's patient had improved markedly nine months after operation, and Fowler's patient was in satisfactory condition one month after operation. Pool's pa-

tient showed remarkable improvement for two months, and at three months was reported as in a less satisfactory condition, but it must not be lost sight of that his patient was a premature child and had developed very poorly. It is emphasized by Wolff that splenectomy should, for the present, be reserved for severe cases of the disease. The milder types improve upon medical treatment, but the severer types die, usually of some intercurrent affection.

Discussion.—An excellent conception of the varied types of disease in which anemia is associated with chronic enlargement of the spleen in children and infants can be obtained from the several papers by Wentworth,¹ who gives excellent reviews of reported cases. Wentworth concludes that the splenic anemia of infancy is a secondary anemia and in no way related to leukemia. He also infers that the adult form of splenic anemia may be a prototype of the splenic anemia of infants. Hutchison² collected 22 cases of the splenic anemia of infancy in patients from nine months to two and one-half years of age. Ostrowsky³ reports 10 cases of his own, varying in age from seven months to two years, with leukocyte counts of from 8000 to 25,000. Carpenter,²⁰ in a review of 348 patients with splenomegaly under twelve years of age, places rickets first and syphilis second in the etiologic rôle. Ashby²¹ concludes that the toxin causing rickets may also cause the splenic anemia of infancy, and that the reported cases vary from those with marked bone changes and small spleen to those with slight bone changes and a very large spleen. Carr²² draws attention, however, to the following facts: First, that in a majority of rickety children there is no splenic enlargement; second, that there is no connection between the severity of the rickets and the size of the spleen, or the degree of the anemia; third, that in certain cases of the splenic anemia of infancy there is no evidence whatever of rickets. The general experience seems to indicate that, granted the frequent association of rickets, there are yet certain cases which, on account of their marked splenomegaly and their severe anemia, their evidences of extensive blood destruction, and a reversion to

the fetal type of hematopoiesis should, for the present at least, be grouped together as a separate disease entity.

Reports of cases of the adult form of splenic anemia occurring in children under two years of age are very difficult to find, while the splenic anemia of infancy seems practically never to be present in patients over the age of two and one-half years. This observation is in itself suggestive of the possibility that some relationship may exist between the two diseases. The chief clinical distinctions between the adult form of splenic anemia and the splenic anemia of infancy are in the blood picture, and chiefly the characteristics of the leukocyte count. In the splenic anemia of infancy there is more evidence of blood destruction than in the splenic anemia of adults; the red-cell count is likely to be lower, and the color index consequently higher, and normoblasts and megaloblasts are present in the blood-smears. In the adult form of splenic anemia there is an absence of leukocytosis, while in the splenic anemia of infancy there is a notable leukocytosis, which is, however, in reality a lymphocytosis. Our knowledge concerning the normal blood of infants and the reaction of the infant's blood to various toxic agents would lead us to regard these differences as less surprising. And especially does the biologic fact that infancy is a transition period, in which there may be reversions to the fetal type of hematopoiesis, have a bearing upon the variations in the infantile type of splenic anemia. In addition to the above characteristics, we now have also the knowledge that splenectomy has been followed by excellent results in both conditions. These facts would suggest the possibility that the splenic anemia of infancy may be a similar condition to the splenic anemia of adults, and that the differences may be largely due to the peculiar reaction of the infants' hematopoietic system to the etiologic factor in the disease. For the present, and until our knowledge is much fuller, a sharp distinction should be drawn between the two conditions.

SUMMARY

1. The normal lymphocytosis of the infants' blood and the decided reaction to various toxic agents is always to be taken into

account in the consideration of any case of infantile anemia. Infancy is a transition period during which a reversion to the fetal type of hematopoiesis is likely to occur.

2. The adult form of splenic anemia as it occurs in children and the splenic anemia of infancy have many characteristics in common, and also certain distinctive differences.

3. There is sufficient evidence to indicate a close relationship between the adult form of splenic anemia as it occurs in childhood and the splenic anemia of infancy. Until our knowledge is fuller, however, a sharp distinction should be drawn between the two diseases.

4. Splenectomy has been performed in only a few instances of the adult form of splenic anemia occurring in the first decade of life. One case of this character is reported herewith. There is a doubt as to the exact diagnosis in some of the seven cases collected from the literature.

5. A review of the literature of the splenic anemia of infancy (anæmia pseudoleukæmica of von Jaksch) shows that splenectomy has been performed in four instances of severe types of the disease, with marked immediate improvement.

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THE RELATION OF THE SPLEEN TO CERTAIN ANEMIAS *

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The story is told of a professor of physiology who asked a medical student what was the function of the spleen, and received the reply, "I did know but have forgotten." The professor said: "It is a great pity you have forgotten, because no one else has ever known." Recently, however, as a result of the study of the pathology of the living, largely from material obtained at the operating table, more accurate knowledge of the function of the spleen has been gained, although in this we are still woefully lacking as compared to our knowledge of the other organs of the body.

THE RELATION OF THE SPLEEN TO THE LIVER AND DIGESTIVE TRACT

The spleen and liver are closely associated in function. The liver is essential to life, the spleen is not. The liver acts as a gigantic means of defense against poisons, both parasitic and chemical, which would otherwise reach the general circulation from the gastro-intestinal tract through the radicals of the portal vein. This is well shown in cancer of the rectum and intestine, which, through the portal circulation, often develops embolic processes in the liver, though seldom in the lung. Cancer of the stomach, on the other hand, by reason of direct communications with the general circulation through the diaphragm, as well as through the portal vein, frequently develops secondary cancer in the lungs as well as in the liver.

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The splenic artery arises from the celiac axis, the same source which supplies the pyloric end of the stomach and upper duodenum, the liver and pancreas, all of which are derivatives of the foregut, and all organs concerned in the proper preparation of food products for digestion and absorption, as in them also the venous return of the spleen becomes part of the portal circulation. The vascular system of the spleen is large and is curiously arranged, inasmuch as the walls of the blood-vessels, except the endothelial lining, are absent and the blood comes in direct contact with the splenic pulp.

The spleen contains a considerable amount of non-striated muscle-fiber and elastic tissue, but only a very scanty supply of nerve tissue, and that largely from the sympathetic. Every organ of important internal secretion is very closely, if not organically, associated with sympathetic nerve tissue. Note the adrenals and hypophysis, part glandular and part sympathetic ganglia. This close relationship of the glandular secretion with the sympathetic nervous system enables wide-spread effect, so that the internal secretions may be said to play on the sympathetic nervous system as the fingers play on a piano. The scanty nerve supply of the spleen shows that it does not produce an important internal secretion. Its function must be closely associated with metabolism, shown by enlargement during the digestive period and contraction following digestion. That these physical changes are brought about through the blood-stream seems assured, since epinephrin solution in the circulation will cause the spleen to contract one-third in size, as noted by Elliott and Kanavel.¹

The idea that the spleen is an obsolete organ of little function is not tenable, as Eccles² has pointed out. The outstanding fact in a retrogressing organ is the reduced blood-supply. The tonsils, for example, were at one time supposed to be retrogressive, but the fact that the tonsil has five sources of blood-supply shows that it is not obsolescent, yet it is not essential to life, and when diseased has great potentiality for harm. This is quite analogous to the spleen.

It would appear that the spleen removes from the circulation not only cellular elements of definite food value, but also, when

unable to care for these products, sends them to the liver for elaboration into energy-producing substances, on the one hand, and destruction of various toxic agents on the other, that nothing of value may be eliminated and that dangerous products, wherever produced, may be rendered harmless.

The relation of all animal life to food supply is of first importance. It is a trite saying that nature abhors waste. The amount of energy nature can produce in the living with a limited amount of food has no imitators in man's handiwork. One must confess that whatever his mental and moral deficiencies, and they are certainly great, as a machine, man has no equal. The degenerated cellular elements from the blood and even the food values of ingested parasites are conserved. It has been shown that the phagocytes of the body depend, to a considerable extent, on ingested bacteria for their nutrition (Hiss³). Stohrs and Adami have shown that the leukocytes of the body pass out on the free surface of the intestine and return loaded with bacteria and particles of fat, and that the pigmented areas of the liver are derived from the coloring-matter of slaughtered bacteria. In the same manner the fluids of the intestinal tract are redistilled in the proximal colon after being used mechanically to float the food products down the small intestine and, that nothing may be wasted, bring them in contact with the *valvulae conniventes*, which are to man what roots are to a tree.

The close association of cirrhosis of the liver with enlargements of the spleen has long been noted. In primary cirrhosis of the liver the spleen is enlarged, and in splenic anemia with splenomegalia the terminal stage shows cirrhosis of the liver. In some cases much difficulty is experienced in determining whether the hepatic cirrhosis is primary and the splenomegalia secondary, or the contrary. Nearly thirty years ago Gregory⁴ rather picturesquely stated that nature had three ways of protecting the organism against noxious agents: First, by absorption, destruction, and elimination through natural processes; second, by encapsulation of such harmful substances as it was unable completely to destroy or eliminate, of which the encysted bullet is a gross example; and third, by extrusion, as in the spontaneous opening and discharge of infective

organisms in phlegmons. It would seem probable that in cirrhosis of the liver the second of these methods was in operation. It has been suggested that in chronic alcoholism, for example, the liver, finally unable to destroy and eliminate, attempts to encapsulate a diffuse poison, and that the contraction of this scar tissue produces the cirrhosis. But cirrhosis of the liver is by no means confined to alcoholics. It is often seen in comparatively young people, and those who have never used alcohol. It probably would not be far wrong to say that certain toxic substances circulating in the blood may be gathered into the spleen and sent thence to the liver for destruction, and that chronic hepatic insufficiency might eventually lead to the production of cirrhosis of the liver, on one hand, and, on the other, show its effect on the spleen, as a splenomegaly with resulting anemia, as, no matter what the cause of the splenic hypertrophy may be, an increased capacity for destruction of the red cells seems liable to develop. Syphilitic cirrhosis of the liver with splenomegalia is an example of the non-alcoholic type of disease, and splenectomy in these cases promptly relieves the anemia, although the spleen itself, on pathologic examination, may show no evidence of spirochetal action.

Certain it is that the removal of the spleen has been of very great benefit in some cases of cirrhosis of the liver, especially of the Hanot type. These experiences, however, have been too recent to enable any conclusion to be drawn, but among the group of splenic anemias in which a greatly enlarged spleen has been removed and cirrhosis of the liver was present with ascites, etc., patients have been apparently cured, and the cures have now lasted long enough to enable us to say that at least the cause of a progressive and heretofore fatal malady has been removed. We could not expect a cirrhotic liver to return to normal, but the progress of the cirrhotic process has been interrupted and the remaining hepatic tissue has been sufficient to carry on function. Of the important organs of the body, the liver is one of the few which has the power of regeneration. If half of the liver of a dog be removed, it will be restored in a few months. In the kidney, regeneration does not take place. It is rather hypertrophy of the original tissue of the kidney than

a true reproduction of lost tissue from existing tissue which occurs under similar experimentation.

If we accept the idea that the spleen removes from the blood noxious agents, are we to conclude that all the circulatory blood must go through the spleen for this purpose; or is there an attraction between organs and the arterial supply of the body, that is, do certain organs definitely attract substances circulating in the blood? Rosenow⁵ has shown, for example, that the streptococci cultured in the gall-bladder are definitely attracted to the gall-bladders of experimental animals when injected into the circulation. This is also equally true of other organs—the appendix, the stomach, etc., so that he has been able to produce definite infections of organs with injections of bacteria properly cultured.

THE RELATION OF THE SPLEEN TO THE BLOOD

The spleen is found in all red-blooded animals. The ancestral blood-corpuscle, from which both red and white have their origin, is probably the mesenchyme cell, a form of lymphocyte which appears first in the fetal blood. The most primitive blood is therefore white blood. This is found in the fetus before the red blood appears. All animals that have only one kind of blood have white blood. As the scale of animal life ascends red blood begins to appear, and nearly all the conditions of the blood of the different anemias is the normal blood of some of the lower animals. In fetal life all the lymphoid and adenoid structures of the body, the bone-marrow, the spleen, and in its early stage, probably also the liver, are blood-forming organs. The liver loses this function long before birth. In leukemia all these primitive organs, including the spleen and liver, for some unknown reason, begin to produce embryonic white blood, just as in cancer there is an unlimited production of embryonic epithelial cells, and in sarcoma of embryonic connective-tissue cells. After birth, the spleen continues to produce a certain number of leukocytes, as shown by the fact that the splenic vein contains a higher percentage of leukocytes than the other veins of the body, but does not produce erythrocytes. Osler⁶

states that after severe hemorrhages the spleen may temporarily produce red cells.

It has also been definitely shown that worn-out red corpuscles are strained out in the spleen and destroyed; thus the splenic vein contains a higher percentage of hematin than other veins of the body. In disease we may surmise that excess of splenic function destroys red corpuscles which are not worn out, and the condition becomes one which we speak of as splenic anemia or hypersplenism, and that the exceedingly rare condition of excess of red cells in the blood called polycythemia may be due to deficiency of function of the spleen and associated organs—a hyposplenism.⁷ This explanation, however, is undoubtedly too simple and does not take into account the possibility of the spleen interfering in some unknown manner with the production of red cells in the bone-marrow. It is more probable, however, that in certain conditions of disease red cells are sensitized in other tissues, as shown by the increased fragility of the red cells (Chauffard⁸ and Widal⁹), and are then destroyed in the spleen. Since, when the spleen is removed in cases of primary anemia, pernicious anemia, and in hemolytic jaundice, it is found crowded with disorganized erythrocytes, this hypothesis seems the more logical.

Of great significance is the knowledge that the spleen, and possibly other organs, of themselves not necessary to life, may be *the* link easily broken in an otherwise fatal chain. From the fact that the spleen is not necessary to life, and yet that its removal may definitely check certain hopelessly progressive blood dyscrasias, one must conclude that the spleen is not the cause, but rather the agent of destruction, as in hemolytic jaundice, and that when the spleen is removed, the noxious substances are rendered innocuous elsewhere under more favorable conditions, although what becomes of these toxic agents after the spleen is removed we have no means of knowing. Be this as it may, clinical experience has definitely shown that many of those anemias associated primarily with an enlarged spleen and secondarily with cirrhosis of the liver are definitely cured by removal of the spleen.

ANEMIAS OF POSSIBLE SPLENIC ORIGIN

In grouping these anemias much difficulty is experienced, and the accepted terms of designation concern, to a great extent, syndromes.

Splenic Anemia.—The group called the splenic anemias shows rather a definite clinical picture, for example, secondary anemia, leukopenia, enlarged spleen, hemorrhage from the stomach, and, in the late stages, the characteristics described by Banti,¹⁰ cirrhosis of the liver, ascites, etc., a disease most common in young adults. Children, however, are not infrequently subject to the disease of the adult type, and it is possible that the "pseudoleukemic anemia" of infants, or von Jaksch's disease, is also a manifestation of the same condition (Giffin¹¹). In von Jaksch's disease there is a leukocytosis which is chiefly a lymphocytosis, together with a diminution of erythrocytes, a large spleen, and cachexia. In this condition infants, for physiologic reasons, usually show an excess of leukocytes up to 30,000 or more, older children more often developing the condition seen in adults with leukopenia, but even in adults the leukocytes may be in excess in otherwise typical cases of splenic anemia.

In our clinic to September 20, 1915, 71 splenectomies have been performed, with 6 deaths. Twenty-nine were in cases of definite splenic anemia. All the patients recovering from the operation, with 5 exceptions, have remained quite well in spite of the fact that some were in the late stages of the disease, that is, markedly advanced hepatic cirrhosis, ascites, and jaundice (Giffin¹²).

Gaucher's Disease.—Gaucher's disease or large-cell splenomegalia is closely associated with splenic anemia, and early removal of the spleen will probably cure the condition. Gaucher's disease is characterized by a slowly growing spleen, which eventually becomes a great size, with secondary anemia and, in the terminal stages, the characteristic endothelial growths appear in the liver, lymph-nodes, and bone-marrow. According to Brill and Mandelbaum,¹³ it always begins before the thirteenth year, and averages

twenty years before a fatal termination, usually a terminal complication.

Hemolytic Jaundice.—That hemolytic jaundice, in the great majority of cases, is due to hypersplenism may now be accepted. Whether the spleen is acting on its own initiative or through stimulation of the blood in destroying the red cells we have at present no definite knowledge.

Five patients with hemolytic jaundice have been operated on in our clinic. None of these cases was of the familial type, though all had begun in childhood. In this condition there is an enlarged spleen and constant moderate jaundice of the acholuric type; that is, there is bile in the stool, absence of itching of the skin, and freedom from all symptoms of obstructive jaundice. Usually there is increased fragility of the red cells and an excess of urobilin and urobilinogen in the urine, but no bilirubin. Exacerbations are often preceded by typical crises somewhat resembling gall-stone colic, with increased temperature, malaise, headache, loss of appetite, and an increase of the jaundice. During the crisis the spleen is enlarged and tender. In three of our patients, two under twenty years of age, gall-stones were present. Improvement after splenectomy in our cases was a most remarkable phenomenon. The jaundice began to clear within twenty-four hours following the splenectomy and in four days had wholly disappeared, with complete restoration of well-being.¹⁴

There have been attempts, more or less successful, to demonstrate essential differences between the familial hemolytic jaundice of Minkowski¹⁵ and the acquired disease of Hayem¹⁶ and Widal.⁹ Chauffard⁸ says that in the congenital type the disease shows itself more or less distinctly from birth, and the patients are "more icteric than sick," while the acquired type begins in adolescence and the patient is "more sick than icteric." The congenital type may last for a lifetime with the patient in fair health; the acquired type is progressive and leads to death through anemia and its complications.

There is a remarkable similarity between cirrhosis of the liver with enlargement of the spleen and splenomegalia with cirrhosis of

the liver. Just so are we impressed by the similarity between acquired hemolytic jaundice and Hanot's cirrhosis of the liver. Both are more common in young adults and are more or less chronic in their course, the patients with hemolytic jaundice frequently living out a life expectancy, and those with Hanot's cirrhosis lasting from four to ten years. Both have enlarged spleens accompanied by jaundice, often slight, but with exacerbations; both may have crises marked by pain in the region of the liver, and in both ascites is usually absent. It is very evident that there is some connection between hemolytic jaundice and Hanot's cirrhosis. That hemolytic jaundice is definitely cured by splenectomy can be stated as a fact, and growing experience leads to the conclusion that improvement and sometimes definite cure in Hanot's type of cirrhosis of the liver may be effected by splenectomy, although in confusing types of the disease with hemophilic tendencies one must be guarded in advising surgical treatment.

Pernicious Anemia.—It has been known for many years that pernicious anemia is often accompanied by a large spleen. Eppinger¹⁷ first pointed out that after the spleen was removed in pernicious anemia an extraordinary improvement in the condition of the blood was usually noted, and experience has borne out Eppinger's observations.

Cabot,¹⁸ in discussing six splenectomies for pernicious anemia, said he had never seen such great improvement produced by any medicinal agent as had followed splenectomy; that no medicament with which he was acquainted would bring up and hold the red cells above four million. Four of his patients had been incapacitated for two years or more, and within a few months after splenectomy they were able to go back to work. He points out that sufficient time has not elapsed to show that these patients are cured, but even as a means of producing a prolonged interval of well-being the splenectomies have been worth while.

It is true that the spinal cord changes in pernicious anemia have not been benefited by splenectomy, and they have even progressed after splenectomy in spite of the general improvement of the patient. Also the blood in the splenectomized patients so far

observed did not entirely lose the characteristic pernicious cells, nor could we expect it to do so. We cannot expect the operation to overcome structural changes in organs which have been permanently damaged, and up to the present time the only patients who have been subjected to operation have been largely those in advanced stages of the disease. Experience shows that splenectomy should be resorted to early, and in these cases cure may at least be hoped for. The spleen has been removed in 12 of our cases of pernicious anemia (September 20, 1915). The improvement in some of these has been remarkable, but not enough time has yet elapsed to warrant any definite statements being made.

In reviewing the basic facts of splenic anemia, hemolytic jaundice, and pernicious anemia, the one fact that stands out is that there is a destruction of the red blood-cells and that this hemolytic change is accompanied by physical changes in the spleen. It is interesting in this connection that in 16 of the 71 cases of splenectomy in our clinic gall-stones were found, and all were in the groups of anemias (47 cases).

In addition to these rather definite groups of cases, enlargement of the spleen is found under conditions for which, through lack of knowledge, we have no ready classification, as in certain diseases with hemophiliac and purpuric tendencies, and it may eventually be shown that the spleen is associated with these conditions of the blood. Patients with anemia associated with splenomegalia and having high temperature, such as are seen in the pregnant state, require further study. I shall not discuss infections of the spleen, bacterial and protozoal, which give rise to surgical conditions, nor those anomalies and tumors of which we have observed some remarkable examples. I have purposely omitted reference to the pathology of the spleen itself, because this is not as yet sufficiently advanced to be more than suggestive. Wilson¹⁹ is now studying our cases, and is able to show that there is a true microscopic pathology in these diseases which it is hoped will prove to be characteristic.

Our knowledge of splenic disease, like most of our knowledge of organs in concealed situations, has been the result of study of

living pathology under surgical conditions. Postmortem examinations, which were once looked on as the final word on disease processes, have too often not shown the chronic diseases from which people suffered during life, but only the disease from which they died. Experimentation on animals, like the postmortem, has been of enormous value in laying a foundation for medicine, but as the animals themselves were not diseased, the conditions favorable to exact knowledge were not present, and experimentation is now seen in its proper light as an aid to understanding, but not as the final solution of problems of the living. But the living pathology brought forth by the surgeon has in this field, as in others, enabled medical research to produce most valuable material for study, and has within the last few years advanced our knowledge of the physiology, pathology, and therapeutics of disease conditions of the spleen more than all else that has been done since the beginning of time.

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SURGICAL CONSIDERATIONS OF SPLENECTOMY *

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Splenectomy.—The safety of splenectomy depends on careful separation of the attachments of the spleen and its delivery without injury to the vascular pedicle. Therefore much depends on the size and movability of the spleen, and the amount and vascularity of its adhesions, as well as on the thickness of the abdominal wall.

Incision.—Bevan,¹ in 1897, described a most satisfactory incision for operations on the gall-bladder and biliary passages which has been modified by various surgeons. A longitudinal incision is made through the upper rectus muscle, extending obliquely along the costal margin, about an inch and a half from it and up toward the ensiform cartilage. The longitudinal part of the incision may be carried down to any desired length, permitting careful abdominal exploration. In this respect its value in operations on the biliary tract is very marked, as an appendix may be removed or any necessary operation may be performed on the pyloric end of the stomach or duodenum. The incision made on the left side is equally advantageous in gaining access to the spleen. In working in the biliary region the longitudinal part of the incision is best made in the inner half of the rectus muscle; for splenectomy it is best made in the outer half. If the incision across the rectus muscle is kept an inch or more from the costal margin, this little flap, when caught with a catspaw, makes an excellent retractor.

Adhesions.—In most cases in which splenectomy is necessary, the spleen is enlarged and adherent to the partial peritoneum and

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diaphragm, especially over the upper pole. These adhesions differ greatly in their vascularity, being occasionally purely vascular,



Fig. 135.—The Bevan incision for splenectomy, shown in upper figure. Lower figure—method of using gauze pack for temporary hemostasis to control bleeding of separated adhesions.

composed of a small artery and one or more varicose veins. Since these vessels cannot be seen and controlled until the spleen is

loosened from its bed and drawn down, it is usually best to separate them with the fingers as close to the spleen as possible, trusting the control of any hemorrhage to a large gauze pack until the spleen can be delivered and removed (Fig. 133).

At times the spleen is firmly fixed in position by adhesions so strong they must be divided by a cutting instrument. By making an opening in the adhesions close to the splenic capsule and loosening the spleen as far as possible by a combination of enucleation and division, a very adherent spleen may safely be removed.

A subcapsular splenectomy, in the sense one speaks of a subcapsular nephrectomy, is not possible. The capsule of the spleen is closely associated with the splenic pulp, which is lacerated in the attempt to remove it from within the capsule, causing great loss of blood. With a little care, however, the spleen can be separated immediately at the capsule, leaving the attachments in a condition so there will be comparatively little bleeding. In this way the spleen can be quickly delivered and the pedicle temporarily controlled by fingers or an elastic, rubber-covered pedicle clamp. The main thing to be accomplished is to leave the separated attachments in such condition that a gauze tampon will temporarily prevent bleeding. In two cases in my earlier experience the spleen was so firmly fixed with vascular adhesions I did not deem it wise to undertake splenectomy.

Separation of the Splenic Ligaments.—Much may be learned concerning the normal relations of the spleen by operative work on the cadaver. The most serious vascular attachments are the vasa brevia in the gastrosplenic ligament which pass to the stomach. However, the bulk of these attachments can be delivered with the spleen, since the stomach can be drawn from the abdomen to a very considerable extent before separating the gastrosplenic ligament. Unfortunately, in a large adherent spleen there may be vascular connections in the deeper portion of the gastrosplenic ligament which pass inward and backward to anastomose with vessels along the spine and the crux of the diaphragm. Since these must be separated before the spleen can be eviscerated, early careful adjustment of an adequate gauze tampon, for temporary control of

hemorrhage, may be essential. The lienorenal ligament has no great vascularity and can be readily divided. After the delivery of the spleen the remainder of the gastrosplenic ligament and a leash of vessels passing to the inferior border of the spleen which connect it with the splenic flexure of the colon are tied in sections. This completes the peritoneal and omental attachments about the hilum, and, by dividing a few adhesions here and there, the spleen can be lifted up so that the vascular pedicle lies completely exposed for at least two inches.

Pancreas.—The splenic pedicle should be searched for the tail of the pancreas, which, if present, will lie in the pancreatic notch of the spleen, behind the hilum. It can usually be readily separated, a few ligatures applied to bleeding points, and then dropped back into the abdomen. In three splenectomies I tied off a portion of the tail of the pancreas with the splenic pedicle, in one case removing as much as an inch and a half, without any harm resulting.² The spleen was bleeding so freely from lacerations that time could not be spared for separation. In the third case, in which the splenic vessels were atheromatous and would not hold a ligature, I tied the splenic vessels together with the body of the pancreas about three and one-half inches from its tip with two ligatures of catgut, three-fourths of an inch apart. The patient recovered without serious symptoms.

The pancreas has five independent sources of blood-supply which protect its circulation. The pancreatic ducts have been shown clinically and experimentally to have great powers of regeneration. Fat necrosis as the result of escaping pancreatic secretion from injury to the pancreas in this situation apparently is not to be greatly feared, probably because its secretions are not activated by duodenal secretion.

Vascular Pedicle.—In the average case the vascular pedicle can be so thoroughly cleared that it may be easily ligated in sections. The artery should be tied first, but all vessels should be tied before any portion of the pedicle is cut. In spite of this precaution the spleen sometimes tears from the pedicle before it can be ligated. This accident happened in one of my cases—a fleshy patient. The

spleen had a short pedicle which retracted deeply, but I was able to grasp the vessels in my fingers and hold them until forceps could be applied. In this type of case it is better to grasp the entire pedicle with elastic, rubber-covered clamps³ which will temporarily compress without damage any attached viscus, such as the wall of the stomach, until the splenic vessels can safely be controlled. In two instances I have injured the stomach because of its close attachment to the splenic pedicle, in one case ligating a portion of the wall of the stomach in the pedicle. Fortunately, there was no escape of gastric contents and the damage was repaired. The patient recovered. In the second case I was less fortunate. There were large varicose veins in the gastrosplenic ligament and, in making a thorough exposure of the pedicle, one of the veins in the wall of the stomach was torn. Unfortunately, tooth-forceps were used to grasp the vessel and the fragile gastric wall was lacerated. There was an escape of gastric contents into the bed from which the spleen had been enucleated, and the patient died a few days later from sepsis.

When the vascular pedicle has been carefully exposed, but is too short for accurate ligation of the vessels, the two-forceps method will be found very satisfactory. In this procedure two forceps are placed three-fourths of an inch apart on the pedicle, and the spleen is cut away without regard to back bleeding. A catgut ligature is thrown around the pedicle, below the proximal forcep, which is then loosened, and the ligature tied in the compressed area, while the distal pair of forceps steadies the pedicle and prevents retraction. A second ligature makes the pedicle secure.

There are undoubtedly some cases in which splenectomy is indicated, but in which the condition of the patient or the attachments of the spleen make the operation inadvisable.

Two years ago I³ suggested the possibility of ligating part of the vessels, believing that it would have an effect comparable to the ligation of the thyroid vessels in hyperthyroidism. I have not had an opportunity to carry out this suggestion, and am not at all sure that it could be done with any degree of accuracy unless the

delivery of the spleen were accomplished, and in that event splenectomy would be equally easy and more effectual.

John Gerster⁴ has suggested ligation of the splenic artery at the celiac axis as a preliminary step in splenectomy, or in some cases as a method of producing atrophy of the spleen when it would not be practicable to remove it. He has mentioned the ease with which the celiac axis can be reached through the gastrohepatic omentum. The splenic artery certainly could be conveniently tied at the celiac axis, or just where it lies at the superior border of the pancreas.

Experimental ligation of the splenic artery demonstrates that the normal spleen will not become necrotic, but that it will undergo atrophy. The blood supply from the splenic artery to the pancreas and stomach which would be cut off by ligation is not important and would be well taken care of from the numerous anastomotic branches of other sources.

Closure of the Splenic Space.—This procedure is exceedingly important. Compression with the large temporary tampon will enable the smaller vessels to become sealed in a few minutes, but in the deeper recesses of the wound there will probably be vessels requiring other treatment. With catgut on a small curved needle, the raw space, beginning at the tied splenic vessels, is closed as well as possible. The margin of the lienorenal ligament, on the outer side, is sufficiently firm to hold a suture, but on the inner side such bits of tissue must be caught here and there as can be done safely until the bleeding vessels are compressed. The last sutures come well down on the diaphragm and had best be applied during cardiac diastole and during expiration. In some cases the splenic space will be dry when the tampon is removed and suturing is not necessary. To be able to leave the wound dry is a great satisfaction and well worth the little extra time taken to accomplish it. One of my patients died of so-called secondary shock, due to failure to control hemorrhage at a deep point, and in two of my earlier cases, before I understood the value of the snaking catgut suture, I was compelled to leave a large tampon to control the oozing (Fig. 134).

Drainage is not needed unless there has been injury to some viscus. The after-care is quite the same as that following any abdominal operation.



Fig. 134.—Closure of splenic space by snaking catgut suture, to control oozing of blood from deep-seated areas.

Mortality of Splenectomy.—The mortality of splenectomy depends more on the type of case accepted for operation than on the

technical difficulties of the operation itself. If the patient is in good general condition, a small, movable spleen can be removed with a death-rate so low as to be almost accidental. If the spleen is enlarged, but has considerable latitude of motion, splenectomy may be performed with almost no mortality beyond the possible accidents of a serious operation. But if the spleen is enlarged and adherent and the patient is suffering from a high grade of anemia with myocardial and renal changes, marked by edema of the lower extremities, or is suffering from ascites, jaundice, high temperature, etc., the mortality will necessarily be high. Even under these conditions surprisingly few patients die directly as the result of the operation. In 14 of our patients edema of the lower extremities was marked. Seventeen had ascites with coincident myocardial and renal changes, 7 were jaundiced, and 5 were suffering from high temperature at the time of the operation. There were many combinations of these conditions, all in connection with high grades of anemia, yet there were but 5 deaths in the hospital from all causes in the 58 cases operated on. As shown by the postmortem, 2 of the 5 deaths were from preventable causes (hemorrhage and sepsis). In conclusion, I desire to express my early indebtedness to J. Collins Warren⁵ for his splendid paper, "Surgery of the Spleen," stimulating interest in the subject.

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HEAD, TRUNK, AND EXTREMITIES

HYDROCEPHALUS, SPINA BIFIDA, AND ALLIED DISEASES *

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Hydrocephalus, spina bifida, midline nerve and cystic tumors of both the head and the spine constitute one of the most serious types of congenital deformities. In hydrocephalus there is usually great impairment of the development of the brain, and with spina bifida there are often associated paralysis and great disability. The natural and surgical mortality is high in all these conditions, the protruding sac being favorable for operation only when the condition is uncomplicated. The more advanced cases, with involvement of the nerve tissues, are only partially cured by surgical measures, even though the sac be ablated, while a marked degree of hydrocephalus is still beyond our ability to cure, although some cases are apparently benefited by surgery. As all these conditions are brought about by an increase in the tension of the cerebrospinal fluid, a single individual may present one, two, or three of these conditions, which have developed by pressure.

Cerebrospinal fluid is formed as a secretion from the choroid plexuses. This fluid passes through the main iters which connect the various ventricles, and filters through the thin membranes of the brain and cord, equalizing the pressure at all points. To maintain equilibrium of pressure, the absorption is carried on by the Pacchionian bodies and a limited lymphatic system, the great bulk, however, being carried by the veins of the arachnoid space.

An increase in the tension of the cerebrospinal fluid may be caused by tumor of the brain or by infections of the brain and men-

* Reprinted from *International Clinics*, 1915, ser. 25, iv, 286-292, courtesy of J. B. Lippincott Company, publishers.

inges. This has been experimentally produced by blocking certain iters and by the injection of irritants into the ventricles. It is well known that hydrocephalus may be arrested at an early period, but there remains a manifest change in the size and appearance of the head. Numerous instances are reported of brilliant men with partial hydrocephalus.

CLASSIFICATION

A classification of hydrocephalus on anatomic grounds is hydrocephalus, cephalocele, meningocele, anterior and posterior, and hydroencephalocele.

Of the spinal lesions, there are extreme maldevelopment with openspinal cord throughout more or less of its length, called *rachischisis*, the skin, bony arches, and meninges all being absent. *Anencephalia* sometimes accompanies this condition. *Spina bifida* may also be partial, involving only a few vertebræ. At the defective point the cord at the central canal may be open, and is then called by von Recklinghausen the "area medullovasculosa," having the appearance of mucous membrane. In less severe forms the defect is covered by a thin membrane, the central canal being connected with the skin, at which point a leakage of cerebrospinal fluid occurs. Infants with such deformity are still-born or life is short.

Myelomeningocele is the most frequent type of *spina bifida*, and represents about four-fifths of the cases. It is usually accompanied by disturbances of the nerves of the legs and varying degrees of paralysis, according to the extent of the involvement of nerves in the outer tumor mass. This may include the control of the sphincters of both bowel and bladder. The thin, glistening sacs of these tumors are often seen moistened with the sweating of the cerebrospinal fluid. Unless operated on, the majority of children in this condition die during the first years of life.

Spinal meningocele in the lumbosacral region, the location of about 86 per cent. of *spina bifida*, is found in about 10 per cent. of cases reported. The sac consists of dura and contents and none of the cord or nerve tissues.

Syringomyelocele is not common. In this condition the cerebrospinal fluid in the central canal has distended the lower segments of the cord, and prevented the development of the spinal laminæ.

A very rare form also is anterior or ventral spina bifida, a protrusion between the halves of the bodies of the vertebræ, the tumor showing in the abdomen or pelvis, more commonly in the latter, with some defect in the development of the sacrum caused by the pressure of the meningocele. Most of the cases reported of the anterior type were in females.

Spina bifida occulta is that condition in which there is a posterior bony opening which remains through life, but without protrusion. Such are noted in young adults and also in middle life as thickened areas of skin covered by excessive hairy growth. These flat-surface tumors have occasionally been operated on in the belief that they were lipomas.

ETIOLOGY

There has been much discussion as to why spina bifida should develop. Looked upon as a congenital defect, it was difficult to attribute a cause for it. Some theorists claimed it to be due to adhesions posteriorly of the amniotic sac; others claimed it was a true germinal defect, the cause of which could not be explained. It is now generally accepted that adhesions found in congenital deformities are caused by the malformation instead of the adhesions causing the condition.

Hertwig¹ showed that a 0.7 per cent. solution of sodium chlorid used in treating the egg of axolotl quite generally caused spina bifida of the embryos, and this was accomplished also in frog embryos at an early stage of development when placed in 0.6 per cent. solution of sodium chlorid (Morgan and Tsuda²). Nearly all the experimental evidence of recent years shows that the increased secretion of the choroid plexus is undoubtedly the cause of the development of these conditions. Sharpe's³ experiments, in which he caused increase of the spinal fluid and removed posterior segments, exposing the spinal cord by laminectomy, showed quite

strikingly the possibilities of the bulging cord preventing the development of the laminæ. Dandy⁴ stopped the outflow of fluid from the ventricles by plugging the iters, then injected a solution of phenolsulphonephthalein into the ventricles, and in some cases into the subarachnoid space, proving that this fluid is absorbed mostly by the blood-vessels of this space. Förster⁵ stated long ago that a dropsical condition of the central or neural canal probably occurred in some cases of spina bifida. The defect should occur before the third month, as the development has then proceeded so far that the ventricles and spinal canals are sufficiently formed to contain cerebrospinal fluid.

Much enlightenment may be thrown on the subject of congenital defects and deformities by a study of the comparative anatomy of the vertebrates, but it is not to be compared with what may be learned by a study of the invertebrates. The great changes in animal life occurring in the past ages have been brought about by some remarkable change at a given period in the predominant type of the animal, and this change has been of a degree to permit the animal to change the media in which he lived and his manner of taking nutrition. In the line of these changes may be found the cue for the explanation of defects in development, and, since the remarkable changes of the vertebrates over the invertebrates have been in the development of the nervous system, and, consequently, of the digestive system, it is along these lines that anomalies are frequently seen.

Man's superiority, and, in fact, that of all the vertebrates in general, are shown early in embryonic life by the enormous development of the nervous system compared with the size of the embryo. His superiority also makes him subject to the greatest number of errors in development following the cleavage lines of life's progress. Great changes have also come about through the modifications in methods of nutrition and elimination. The invertebrate animals are characterized by having a cephalic stomach and a single straight gut, and otherwise differ from the vertebrates in that their nervous system is in front of the intestinal canal and that their central nervous system surrounds the mouth. In the primi-

tive forms there is only the ring of nervous tissue around the esophagus; in higher development the paired segmentation of nerves occurs below the esophagus and there is muscular development. Above the esophagus the optic and olfactory nerves develop, and with the development of the cerebrospinal and special-sense nerves the nerve-mass grew up over the cephalic stomach, a condition which made a natural limitation to the progress of these higher types of invertebrates; *e. g.*, the limulus, sea scorpion, king crab, etc. Thus the more brains they developed in order to secure food, the less was their ability to ingest it. Certain of these developed claws and mandibles to hold their prey and became the natural blood-suckers of the world, living on the highest type of food, the limited digestion of which was aided by digestive gland-cells, liver, and pancreas, which are located on the wall of the cephalic stomach, between the areas covered by nerve tissue.

In the transition from invertebrate to vertebrate the animal did not turn on his back so that the intestinal system should be ventral to the nervous system, but the whole plan of life was changed, especially for the maintenance of nutrition and to enable the nervous system to become predominant. Along other lines of development it is well known how in some amphibia the swimming bladder came from the primitive lungs; others respired by the skin. In another period the intestinal tract developed from the yolk-sac by ventral closure. The cephalic stomach became the ventricles of the brain, while the nervous system grew up around and enclosed the straight gut, the base of the skull and spinal system developing from the notochord in front of it; thus the straight gut in the human embryo became the neural canal, which communicated at the caudal end with the rectum, closing in about the third week. In rachischisis the neural canal fails to close; thus we have anencephalia and the separated halves of the open cord. The infundibulum withdraws within the skull, taking with it the pituitary, or former mouth-gland, which, with the thyroid, is still active in controlling assimilation, deposit of fats, and stature, having also sex characteristics. The thyroid changes from a duct to a ductless gland and passes into the neck. Consequent to these extensive

changes the early vertebrate embryo has no mouth, but in the evolution there is the beginning of a cavity called the stomatodeum, which quite early becomes connected with the foregut through a breaking of the membrane formed by the endoderm and ectoderm. The proctoderm does the same thing at the caudal extremity, uniting the rectum with the skin. In this latter region, also, many deformities occur through defects of development. As the gray matter covers a considerable area of the cephalic stomach in higher invertebrates, in the vertebrates, when it becomes the ventricles, the patches of gray matter come together to form the cerebrum. The membranes, formerly covered by digestive gland, infold into the ventricles, thereby developing the choroid plexuses.

This brings us a step nearer to the cause of the formation of excessive fluid. Is it due to a remnant of the digestive gland immediately along the line of the choroid plexuses that has become stimulated in the embryo by some changes in the sodium salts? This would be quite possible, as all animal life originally lived in this medium (sea-water). Or was the stimulation chemical by the food acting on the remains of such glandular material in the early period after birth and leading to increasing secretion?

TREATMENT

Much has been written on the treatment of these cases. In hydrocephalus treatment is most unsuccessful; yet certain cases do not progress either untreated or after surgical interference, and such therefore may show a high percentage of success in apparently stopping the growth. Puncture of the corpus callosum or ligation of the carotids may rarely be successful. Various means of external and auto-drainage, tubes, setons about the brain, and intraperitoneal drainage around and through the body of the vertebræ have shown remarkable instances of how much and how long these defective children will survive surgical intervention.

The sac of spina bifida has been considered an entity, and wonderful procedures have been recorded of the removal of the sac and of plugging the opening, both homoplastic and heteroplastic bone-grafts being used. Such operations, or even simple removal of the

sacs in spina bifida which is stationary, will give a fair percentage of success, but if made on one which is growing the child is quite likely to die of cerebral pressure or later develop hydrocephalus,

Division of membrane,
incision surrounds neck of sac

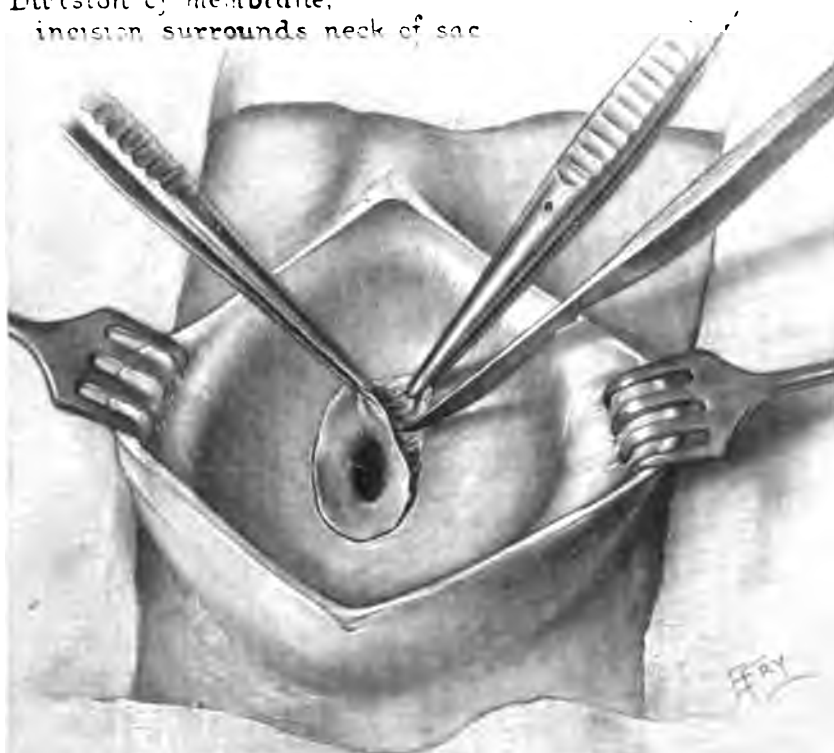


Fig. 135.—Longitudinal division of sac. Membranes of the opening dissected from subjacent tissues.
(From "International Clinics," J. B. Lippincott Co., publishers.)

since the sac is acting as an elastic bulb. In some cases the sudden relief of tension of the cerebrospinal system may stimulate a rapid outpour of fluid, leading to death from intracerebral pressure. Local treatment by injection of irritants, such as Morton's fluid

and other iodine preparations, is rarely employed. In operating on these cases it should be recognized that the sac has nothing to do with the secretion of fluid and is purely a hernia. Operation is advised on the stationary tumor only.

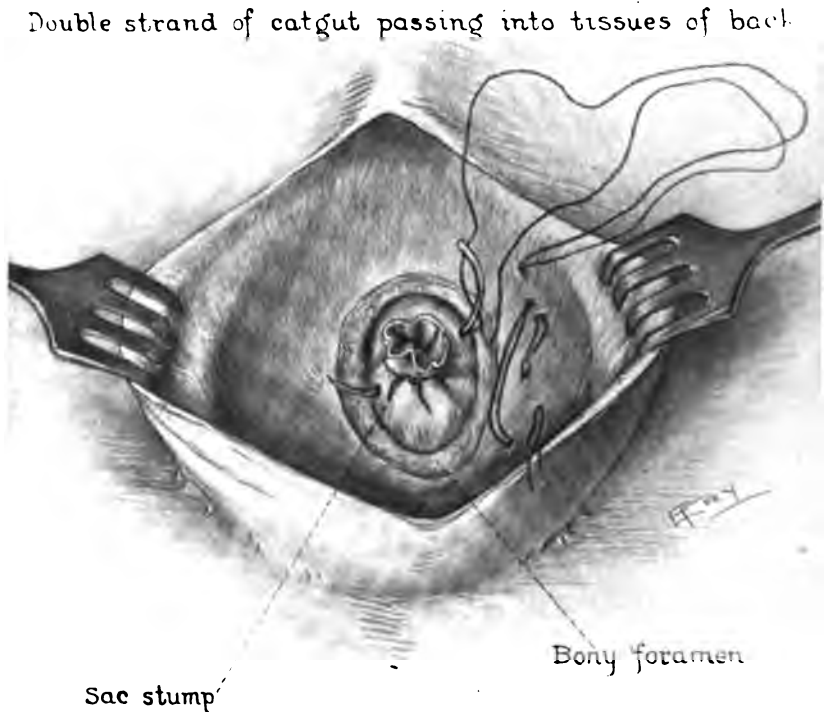


Fig. 136.—A safety method for subcutaneous drainage of the cerebrospinal fluid. (From "International Clinics," J. B. Lippincott Co., publishers.)

In operating, the child is placed on a slanting table, the head sufficiently lower than the spine so that the ventricles will be kept full of fluid. The spina bifida is divided in the midline, paying no

attention to the escape of fluid, and the sides drawn apart. If it is a pure meningocele, a knife or sharp-pointed scissors divides the membrane in a circular manner a quarter or half an inch above the opening, according to its size. The opening is then closed by ligature or suture. With a curved needle a double strand of catgut is

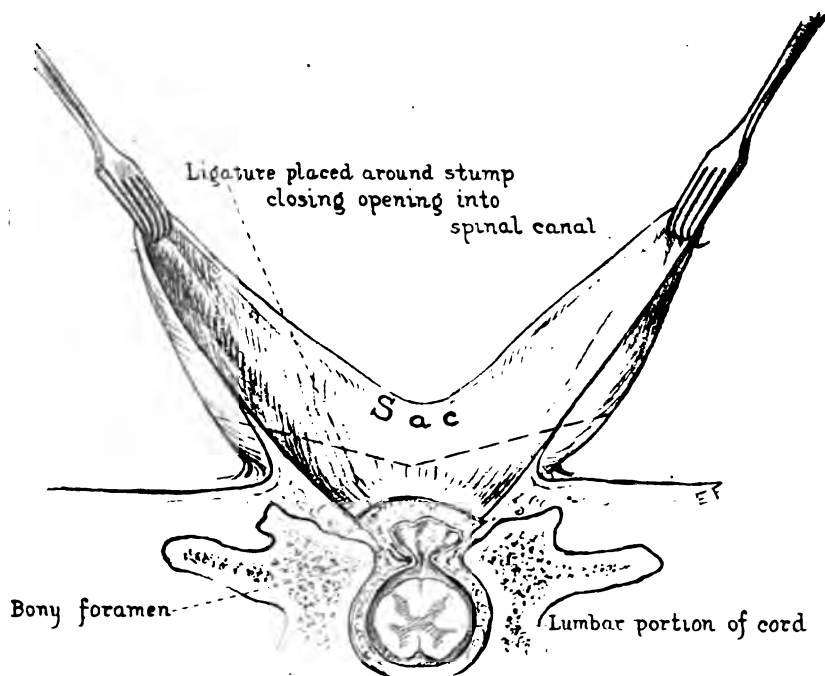


Fig. 137.—Sagittal section of sac. Dash line indicates removal of redundant tissues. (From "International Clinics," J. B. Lippincott Co., publishers.)

passed through the stump so as to tap the contents. The needle is passed about on either side into the tissues of the back with the catgut which fills the needle opening in the stump of the sac, yet under pressure acts as a seton. The child reabsorbs the spinal fluid, thus making a temporary safety valve. The excess of skin is now

removed, permitting adjustment after removal from either wall of the outer part of the remainder of the spina bifida. The incision is closed without drainage (Figs. 135, 136, and 137).

In case of involvement of the cord, when there are varying degrees of paralysis of the sphincters and club-feet, the primary procedure is the same. The congenital deformity, club-foot, is undoubtedly due to a late pressure on the caudal filaments or to detachment of the terminal filaments which attach the neural canal to the posterior region of the coccyx. This relieves some of the tension on these nerves during their development, as the spine, which is originally the same length as the cord and canal, outgrows it by a third.

Club-foot occurring in spina bifida occulta is due to adhesions to the sac of the posterior nerve-trunks to the legs, the overgrowth of the spinal column compared to that of the spinal cord causing a destructive traction. Some operative work has been done in such cases by Jones⁶ and Sever.⁷ The nerve tissues can be seen on the sides of the sac; a circular incision is made above these, and the protruding membrane divided in the midline above and below, the halves being rolled within and covered by a separate flap made from the tissues from one or both sides. So far as the use of bony covering is concerned, there has been a sufficient number of operations on children and of laminectomies in adults to show that transplantation of bone is an unnecessary addition to the operation. Paterson⁸ has shown that when the pressure is removed the laminae tend to develop.

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CIRSOID ANEURYSM *

EDWARD S. JUDD

Most writers believe that the so-called cirroid aneurysm, strictly speaking, is not an aneurysm, but a neoplasm or tumor with a close affinity to angioma; that it is, in fact, a disease acquired or grafted on preëxisting normal arteries. Matas¹ states that the blood-vessels which form a cirroid aneurysm are largely neoplastic, and are frequently reproduced *in loco*, after apparent complete extirpation, and also that veins of new formation participate in the process. In the severe cases it is the middle coat of the arteries particularly which is stretched, the arteries becoming pale and thin and resembling veins during the process of enlargement. The unequal saccular pouches, which are true aneurysms, usually project toward the surface of the skin. As the artery elongates it becomes tortuous, sometimes even spiral. The process is rarely circumscribed, but may attack several trunks and their branches. It often affects the vessels about the scalp and face, more instances having been recorded of its situation in this locality than in all other parts of the body taken together. Originating usually in one of the arteries of the scalp, the process extends to the branches on the other side of the head, and may implicate the connecting vessels to a variable extent. On the other hand, the process may pass into the capillaries, widely dilating them as it progresses, and may even affect the terminal veins. In such event it becomes a racemose aneurysm or an aneurysm by anastomosis. To a less degree the larger branches from which the arteries of the scalp arise may be affected by retrogression, the process passing even into the carotids.

* Read before the Southern Minnesota Medical Association, December 1, 1915. Reprinted from the St. Paul Med. Jour., 1916, xviii, 48-52.

The superficial temporal, the posterior auricular, and the occipital arteries are the most frequently attacked. The tissue surrounding the vessels suffers little injury, but sometimes the subcutaneous cellular tissue atrophies, the skin becomes very thin, the soft parts may be thickened, and in some instances even the bones may be grooved or perforated.

Many attempts have been made to classify cirroid aneurysms; as a rule, the size of the vessel involved has been taken as a basis. The distinction is often a good one, but the variations are too confusing to permit any real classification of the condition.

The cause of cirroid aneurysms or arterial tumors is not positively known. They occur on the exposed surfaces of the body, the head and hands being the most frequent sites. The condition has been attributed either to peripheral or to central disturbance of the vasomotor nerves, causing lack of tone in the muscular walls of the arteries. Arteritis, frost-bites, and blows have also been mentioned as causes. The origin of these tumors may be congenital or the result of the increased growth of cutaneous nevi. Several cases of this type have been cited. This condition occurs most frequently between the ages of fifteen and twenty.

The clinical history of cirroid arterial tumors does not begin with pathologic changes occurring in the terminal arteries. Dilatation begins before there is any appreciable bulging of the skin or pulsation or twisting of the arterioles. At a later period the physical signs are present and the diagnosis is simple. The consistence of the tumor varies with the amount of connective tissue which has developed around the arterioles as a result of the inflammatory process. Pain in these cases is not constant, and is due to the pressure of the growth on the cutaneous nerves. As the tumor enlarges inflammatory changes become more marked. Adhesions and ulcerations occur, and alarming hemorrhages are frequent. In some instances pressure on the calvaria interferes with nutrition of the scalp.

True aneurysms should be distinguished from cirroid arterial tumors by the fact that these tumors are composed of numerous pulsating arteries and veins, and the mass of a true aneurysm is an

isolated enlargement over a large surgical artery. The cirroid tumor usually occupies the scalp. Ligation or compression of the main artery does not arrest pulsations of the mass or reduce the bulk of the swelling. These tumors may not change for years, or they may steadily increase in size and spread by invading the



Fig. 138.

vessels of the surrounding tissue. The thinness of the overlying skin and the rupture of the ampullæ may result in uncontrollable hemorrhage.

Treatment.—Removal by excision of the aneurysm appears to be by far the best treatment for this condition, hemorrhage being controlled by ligating the afferent and efferent vessels. Many other

methods have been suggested, some of which will necessarily be employed when excision cannot be carried out. The various other methods employed are: the ligation of the afferent vessels, the coagulation of blood by means of various injections, the galvano-cautery, the electropuncture, etc., but in the greater number of



Fig. 139.

cases these procedures have not been satisfactory. In multiple cirroid aneurysm of the hand and other extremities amputation has been necessary. In 1901 Wyeth² injected boiling water along the course of the arteries leading into the tumor. Fifteen to 20 minims were injected at each point and caused immediate arrest of the pulsations in the vessels. The injection was repeated, the

needle being inserted into the tumor in such a way as to puncture the outer opposite surface. He reported a case (a woman twenty-seven years of age) in which five ounces of boiling water were injected into a tumor in the region of the temporal artery, with cure of the patient. This treatment would seem to be especially indicated for angiomas about the face, although in our experience the injections have to be repeated many times and results have not been entirely satisfactory. We do not consider it good treatment for cirroid tumors.

It is believed by some observers that, unless the extension or the severity of the disease may endanger the life of the individual, it is better to abstain from operative interference. The aneurysm is not always the source of imminent danger; it may exist for years without any effect other than inconvenience. Compression of the tumor is one of the simplest, and also one of the most ineffectual, modes of treatment. Ligating the temporal and occipital arteries, also the branches of the artery leading to the affected part, has been tried, but without success. Bruns,³ who has emphasized the treatment by ligation, points out that while ligating one external carotid may reduce the supply of blood to the scalp, the external carotid on both sides should be ligated, thus more effectually reducing the supply of blood to the arteries of the scalp. In this way only would the supra-orbital and frontal branches of the internal carotids be capable of supplying blood to this region, and unless the enlargement is situated in the forehead, their influence need scarcely be feared. Posteriorly the blood would reach the scalp only through the ascending cervical branches of the subclavian and muscular twigs of the vertebral artery. Anteriorly there would be some assistance from the connection of the inferior branches of the subclavian artery with the superior branches of the carotid artery.

It may be noted that ligation of the common carotid is not only attended with greater danger, but offers fewer advantages than the same procedure applied to the external carotids. Ligation of the common carotid, however, has the advantage of shutting off the supply of blood through the branches of the ophthalmic, but the

numerous anastomoses of the opposite side continue to supply blood, and for this reason recurrence of the bleeding may take place.

In the Dawbarn⁴ operations about the head, face, or neck for malignant growths, and in block dissections in similar cases, I have frequently ligated the external carotid arteries (one or more at the



Fig. 140.

same time) in elderly people, and have never seen any ill effects due to the procedure. In our experience it has been noted that ligation of the common carotid arteries may be done safely in young people, *i. e.*, those under thirty-five years of age. In cases of hydrocephalus I have ligated one common carotid, then waited a week or ten days and ligated the one on the other side. In these children

there has been no trouble due to the reduced circulation. In two cases of carotid body-tumors the common and external carotids on one side were ligated and a part of the vessels removed. In neither of these cases were there any untoward symptoms following the operation. Ligation of the common carotid in patients past middle



Fig. 141.

life is attended with a great deal of risk. One of our patients, a woman fifty-three years of age, with a carotid body-tumor, was apparently all right for forty-eight hours after the operation, then began to develop symptoms of softening of the brain. She died on the fifth day, and necropsy showed marked congestion, slight

edema of the brain, and thrombosis of the middle cerebral artery. In another instance in which the patient, a woman sixty-six years of age, was suffering with painful, pulsating exophthalmos of the right eye, I placed the Neff gradual occlusion clamp on the common carotid just tight enough to reduce the strength of the pulsations. The left eye had been removed some time before for the same condition. The operation did not apparently trouble the patient, and at the end of a week she was so much improved that she was up and about. Two weeks after the operation the wound opened, and there was a sharp hemorrhage. I assumed this to mean that the metallic clamp had eroded through the carotid or the jugular vein. This bleeding stopped, and she was apparently recovering when a second hemorrhage occurred, which also ceased without interference. Two or three days afterward I opened the incision and caught up the carotid. The clamp had partly eroded through, the blood presumably having come from the carotids. However, there was no hemorrhage, as the vessel was manipulated in putting a ligature about it. At the time the carotid seemed to be entirely obliterated. After the ligation the patient only partially regained consciousness. It was evident that there was softening of the brain, and she died about a week after the application of the ligature to the common carotid.

Ligation of the common carotid was at one time considered the proper procedure for large cirroid tumors. I cite the few instances, however, to emphasize the seriousness of ligating the common carotid, and especially to emphasize the fact that it should not be attempted in elderly people. Ligation of the external carotid is not only a much safer and simpler procedure in these cases, but also more effective, because the vessels affected by this disease come directly from the external carotid. Fifty-one single ligations of the external carotid and 48 double ligations of the external carotid have been done in our clinic without a death. In eight cases in which one common carotid was ligated there were two deaths.

In cases similar to the one herein reported I see no reason why, except in emergencies, these patients should not be operated on.

My own experience with ligations of the carotids leads me to believe that tying external vessels is comparatively safe, and that the excision of angiomas can be accomplished without danger of hemorrhage and without great risk if the vessels that are the main source of circulation of all the soft tissues about the head, face, and neck have been ligated.



Fig. 142.

CASE A64,674.—M. C. B., man, aged sixty-one years, examined February 27, 1912. This man came for examination because of dilated blood-vessels over the head and face. He stated that the enlargement began when he was seven years old, after receiving a bump on the left side of his head. Since then it has gradually increased to its present size. His right eye has been almost closed

for the past year. Two weeks ago, after picking a small scab on his scalp, profuse bleeding started, which had to be controlled by cotton pledgets placed over the vessels; these were still sealed to the bleeding points when he came for examination. Ten years before he had consulted a surgeon in Chicago, who advised him not to have the condition treated as long as it did not cause trouble.



Fig. 143.

There was a large mass over the bridge of the nose, which extended into the right lids, entirely closing the right eye. The dilated vessels passed back through the scalp to the occipital region; there were also several large swellings in the temporal region. The right facial artery was considerably dilated just where it crossed the border of the lower jaw. The routine physical and

laboratory examinations were negative, with the exception of a few hyaline casts found in the urine.

On March 2, 1912, using a small amount of ether and local anesthesia, I tied the right external carotid and ligated the facial artery separately just above the submaxillary gland. This procedure considerably diminished the pulsations in the prominent



Fig. 144.

part of the angioma, but after a few days they were practically the same as before. On March 8th I ligated the external carotid on the left side, under local and ether anesthesia. After this the pulsations in the entire aneurysm practically ceased. The patient was fairly comfortable for a few days, then the skin on the scalp over the aneurysm became red and tense and he complained of great pain. The scalp and soft tissues about the face were very sensitive.

The pain was so great that it was necessary to give morphin almost continually. On March 13th the patient was given a general anesthetic and an incision was made, extending from the bridge of the nose to the occipital region, through the superficial tissues of the scalp, down to the periosteum. The scalp was turned down on both sides, and the dilated vessels, which were filled with dark, clotted blood, were dissected out. There was no tendency to hemorrhage or active bleeding at this time, and the operation was accomplished practically without loss of blood. After removing all the tortuous branches the scalp was sutured together. It was necessary to make a few separate incisions—one or two about the face and one or two in the left temporal region. A part of one flap of the scalp sloughed, and this particular region was quite slow in healing. But this convalescence was entirely satisfactory, and the patient was out of bed in a few days. He was able to go home about three weeks after the operation and has been entirely well to the present time (Fig. 138-144).

Several similar patients have been under observation in our clinic, though none with such extensive involvement as the one I have reported. The other patients have all been cured either by the ligation of the external carotid or some of its small branches.

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EVISCERATION AND ITS SUPPOSED RELATION TO SYMPATHETIC OPHTHALMIA *

CARL FISHER

In surgical as well as medical practice measures of treatment preëminently successful quickly become standardized and removed from the field of controversy. In a matter apparently so simple as the proper method of the removal of the eyeball this is by no means the case, as certain recent discussions have shown. Accordingly, it has seemed worth while to examine the subject afresh, adding what evidence might be available from the material at hand in the Mayo Clinic. This paper is chiefly an examination of the grounds for unfavorable criticism of the operation of evisceration (exenteration) of the globe; since, in the writer's opinion, this has given the best cosmetic results of any of the operations in common use, with the exception of the Mules operation. If evisceration can be shown not to be of itself a cause of sympathetic ophthalmia, its status as the operation of election wherever possible is fixed, since there is nearly a universal tendency among writers on ophthalmologic subjects to regard the Mules operation as a dangerous one. The writer has had no experience with the modification described by Gifford,¹ or the transplantation of fat into the scleral cup (Gradle²). The assumption that evisceration and its modifications give the best cosmetic result is made somewhat dogmatically, since this depends largely on personal judgment. It has recently been warmly supported by Gradle; on the other hand, more recently Greenwood has strongly favored enucleation, with the insertion of a glass globe in Tenon's capsule. Simple enucleation has but little

* Thesis accepted for membership in the American Ophthalmological Society, May, 1915.

support save on the grounds of safety, and in cases of lacerations, neoplasms, and the like.

Does simple evisceration give as sure protection against the onset of sympathetic ophthalmitis as enucleation? There is a wide-spread feeling that it does not. Schieck³ reported a case of sympathetic ophthalmitis following evisceration, and in the discussion Schmidt Rimpler said that he had seen six such cases. Snellen⁴ reported two and Gifford⁵ collected nine. But it is of the greatest interest and importance to note that in Schieck's case and in Snellen's cases (including one case of sympathetic ophthalmitis following enucleation) uveal tissue was found to have been left behind; in other words, the technic was culpable. The cases mentioned by Schmidt Rimpler cannot be judged for lack of important details, as is, indeed, true of many cases reported.

In examining reports of cases of this sort there are certain considerations to be borne in mind. In the first place, had the injured uvea remained in the body long enough to have planted the seed of sympathetic disease, regardless of what operation may have been done on the eye? The large number of cases appearing after simple enucleation justifies the idea that this is an important factor. This minimum period of safety seems to be between nine days and two weeks—in the majority of cases, one month.⁶ In cases of sympathetic ophthalmitis occurring after evisceration of injured eyes performed later than a month after the initial lesion the mode of operation as a cause is certainly to be regarded as open to doubt unless striking improvement follows enucleation of the stump. Again, such conditions setting in sooner than two weeks—to adopt a conservative figure—after evisceration are certainly not caused by the scleral stump. Furthermore, since the great majority of cases of sympathetic ophthalmia appear within the first year after injury, cases appearing later than a year after the operation should not be laid to the operation without consideration; not every iritis or optic neuritis occurring after an injury of the fellow-eye is sympathetic in origin.

In going over the cases reported in the literature, in an attempt to approximate statistical comparison between the prophylactic

merits of the various substitutes for enucleation, the papers by Gifford and by Welton were found to give very careful analyses of the cases reported up to that time. Gifford collected 16 cases of sympathetic ophthalmia appearing after the Mules operation. Of these, he ruled out all but three on the ground that sympathetic ophthalmia might well have followed if the eyes had been enucleated, the eyes having been removed for persistent inflammation. To these I can add two cases, reported since the publication of Gifford's paper, in which sympathetic ophthalmia might have been caused by the operative stump.

Gifford gives three cases following Frost's implantation of a false globe in Tenon's capsule. Of these, he considered the operation as the etiologic factor in but one. I have found no others.

After simple evisceration, Gifford cites nine cases and retains three as valid; to these may be added three apparently valid cases not mentioned by Gifford.

Welton⁷ collected 27 cases up to 1911 in which sympathetic ophthalmia followed simple enucleation, and a number of other cases might be added.⁸ Had evisceration been done in any of these cases, there is little doubt that the operation would have been held responsible. Welton emphasizes the necessity of early enucleation in cases likely to cause sympathetic ophthalmia, since in his series no case occurred in which the eye was enucleated earlier than nine days: beyond that period the length of time between injury and operation seemed to bear no relation to the onset of sympathetic ophthalmia. The average period between injury and operation was one month.

One must agree with Gifford when he says that—"In view of the uncertainty as to the comparative frequency with which enucleation and its substitutes are performed, there is no use in pretending to anything like accuracy in estimating their comparative dangers. . . . I think it clear that statistics, as well as theoretic considerations, show that enucleation as a prophylactic against sympathetic ophthalmia is somewhat surer than any operation in which part of the eyeball or any foreign body is left in the orbit or scleral cavity. I think it is also certain that ordinary or simple

evisceration is safer than Mules' or Frost's operations." In short, it seems to the writer that the most definite evidence we have (Scheick³ and Snellen⁴) goes to show that, after all, the whole difference depends on the thoroughness with which every particle of uveal tissue is removed. Nevertheless one must be mindful of the very large percentage of cases of sympathetic ophthalmia following the Mules operation.

Referring now to our own material: There have been performed (January 1, 1904, to May 15, 1915) 92 eviscerations in cases in which sympathetic inflammation had not manifested itself at the time of operation. Of these, I have information in recent letters or have recently examined 54, counting none of less than a year's standing. These comprised 9 Mules operations, 45 simple eviscerations, no operations of the Frost type.

In 35 of these cases the initial lesion was a perforating injury, and in most of them the eye removed had been painful or irritated. Eight patients had symptoms of sympathetic irritation before operation. In short, they were average cases. The interval between the injury or onset of the disease and the operation varied enormously—from a few hours to nineteen years.

In no case of this series did sympathetic ophthalmia develop after the operation. This includes the Mules operations as well as the simple eviscerations. Four patients whom I have been unable to reexamine write that they have had trouble with the remaining eye. One developed "cataract" one year and a half after operation—an old man having trachoma-evisceration. One complains that his sight has gradually grown weaker since a year after the operation—a Mules operation done ten years ago—and he is not blind, so that probably there is no question of sympathetic ophthalmitis. One young child operated on two years ago for staphyloma following gonorrheal ophthalmia is said to be near-sighted, a condition which came on six months after operation. The fourth had a severe inflammation of the remaining eye, coming on within ten days after the operation. From his handwriting the patient cannot be very blind, and in any case the onset so soon after operation would remove it from the rank of sympathetic ophthalmia

caused by operative stump. The first eye was removed for absolute glaucoma; probably this caused the failure in the remaining eye. Some of the patients who have been reëxamined lately have been found to have minor affections, such as eye-strain from refractive error, chalazions, blepharitis, etc. Many complain of a sore or discharging socket, yet with no trouble of the remaining eye.

In view of such a gratifying record we see no grounds for discontinuing the practice of evisceration. The results of the Mules operation are equally good in our series, but on account of the emphatic opposition to it found in the literature and in personal communications from ophthalmologists, we shall not venture to adopt it. It should be mentioned that in all the Mules operations the optic nerve was cut well behind the globe, which may have been the factor of safety in this series. Gradle considers the modification of the Frost operation (fat in Tenon's capsule) about equal cosmetically to a simple evisceration, and the implantation of fat in the scleral cup the best of all. In the discussion of Stieren's⁹ article there was expressed a general doubt as to the permanence of transplanted fat. In the present state of opinion on the subject every operation, from simple enucleation without suture to fat implantation, will find support among ophthalmologists of good repute. The conclusion of this paper is that, in the experience of the Mayo Clinic, simple evisceration offers the safest means of removing the eye consistent with a satisfactory cosmetic result if exacting care is used to insure complete removal of the uveal tissue. The operation has this further advantage, that patients needing the eye removed will very often consent to evisceration, though not to enucleation; this is due to a curious psychologic attitude which renders the loss of part of the eyeball much less repugnant than the total loss. Enucleation, of course, must be resorted to in many cases; where sympathetic ophthalmitis has set in and removal of the exciting eye is decided upon, enucleation is preferable for legal security, if not on strictly scientific grounds, and the cosmetic results are often surprisingly good.

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CORRECTION OF DEPRESSED FRACTURES OF THE NOSE BY TRANSPLANT OF CAR- TILAGE*

EMIL H. BECKMAN

A large number of nasal deformities resulting from injury are of a depressed type, that is, the injury has crushed the nasal bones so that the bridge of the nose is flattened. The nasal bones are either forced backward upon themselves or separated and pushed out laterally in such a manner that the bridge of the nose is broadened as well as depressed. Many of these, if treated immediately, can be replaced and held with splints. The intranasal splint made of hard rubber and the external splint composed of sheet lead are at times both exceedingly valuable. If such a fracture has been allowed to heal without the bones being replaced, a marked deformity often exists. A very slight deformity of the bone may produce marked disfigurement of the entire face.

Various methods of correcting these deformities have been tried. One of the commonest has been the transplantation of a portion of bone from the anterior portion of the tibia. A great deal has been written within the past few years in regard to the transplantation of bone, fascia, and fat. Scarcely any mention has been made in the literature in regard to the transplantation of cartilage. Adult cartilage can be transplanted from one portion of the body to another under the same conditions that bone is transplanted, with uniformly good results. Transplantation of cartilage differs from the transplantation of bone because it is not necessary for the viability of the transplant that the cartilage should be in contact with other cartilage or bone. We have also found that it is not at

* Reprinted from Surg., Gyn. and Obst., 1915, xxi, 694-696.

all necessary to preserve the perichondrium in order to secure a good result. Experimental work by Macewen in the transplantation of embryonic cartilage shows that young cartilage, when transplanted into the subcutaneous tissues, continues to grow, and in this way a great many cartilaginous tumors have been produced in animals. Davis' work shows that when adult cartilage is transplanted it lives with no apparent growth or change in its composition, up to three months.

We have several cases in which adult cartilage has been transplanted from the rib into the nose for the purpose of replacing a



Fig. 145.—Before operation

defect in the tissues there. Some of these cases have gone two and one-half years with no apparent change in the size of the transplant. The tissue accepts the transplant very kindly, and even in one case of marked infection the cartilage finally healed in firmly. It is not necessary to transplant cartilage immediately. In one instance a portion of cartilage had been removed from the sternal end of the rib for the purpose of transplanting into the nose, but on account of the congested condition of the patient from the anesthetic, pneumonia being feared, the cartilage was placed in salt solution

and confined in a refrigerator for five days. At this time the patient was again anesthetized, the cartilage removed from the salt solution, and transplanted into the nose. Primary union occurred just as if fresh cartilage had been used.

TECHNIC OF OPERATION

If the nasal bones are widely separated, it is best to refracture them and place a lateral splint upon each side of the nose, letting the splint remain for five or six days, in order to procure a suitable



Fig. 146.—Before operation.

narrowing of the bridge of the nose. As soon as it is certain that there are no breaks in the nasal mucous membrane and that the circulation about the nose is again perfect, the transplant can be made. I have followed the custom of taking a portion of the costal cartilage from the seventh rib, since the cartilage is much broader at this point and a good-sized portion can be obtained, still leaving costal attachment between the ribs and sternum. One is often surprised to find that a large portion of cartilage is necessary to remedy an apparently small defect. A wax model of the nasal defect is valuable as a guide in shaping the cartilage, which may be easily

whittled with a scalpel to any desired size or shape. No attention need be paid to the perichondrium.



Fig. 147.—After operation.



Fig. 148.—After operation.

An incision a quarter of an inch in length is made transversely through the skin over the nose, and just between the two inner

canthi at a point where the bridge of the ordinary spectacles rests. There is usually a slight wrinkle in the skin at this point so the scar is not visible. With a periosteal elevator the skin and subcutaneous tissues are elevated from the bone and cartilage straight down the bridge of the nose nearly to the tip. The separation should not be carried laterally on either side farther than necessary to secure room to transplant the cartilage. The transplant is then



Fig. 149.—Before operation

slipped into place, and, as the tissues have been separated only in the midline, the transplant is held in place and is not dislodged to either side. It may be necessary, however, to place a stitch at the upper portion of the transplant to keep it from slipping upward. The small incision is closed with two or three interrupted stitches of horsehair; the wound sealed with cotton and compound tincture of benzoin.

In my first attempt to transplant cartilage into the nose an incision at the rim of the nostril was made, and the cartilage inserted at this point. This method has also been recommended by Babcock. It is not so satisfactory as the method herein described because the dissection cannot be kept exactly in the midline, and consequently



Fig. 150.—After operation

the transplanted cartilage is apt to slip sidewise. The risk of infection is also much greater in the former method. The only infection in our cases was the one in which a transplant was placed in through the nostril. The accompanying photographs illustrate the points in the technic and the results obtained.

ANTRUM TROCAR AND IRRIGATING CANNULA*

GORDON B. NEW

The two instruments herein described were suggested because of the difficulty, first, in securing satisfactory instruments for tapping antra through the lateral nasal wall under the inferior turbinate to drain pus and for diagnostic purposes, and, second, a suitable cannula which could readily be passed into the same opening for washing out the antrum.

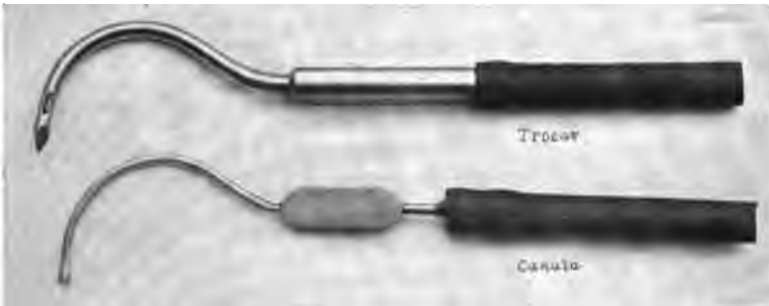


Fig. 131.

The trocar is a sharp-pointed, curved tube with but one opening running along its entire length, and with no channel for return flow. There are two openings, one on either side of the point of the trocar. A heavier portion is at the opposite end to give more strength and a handle to the instrument. To this is attached a piece of rubber tubing. The trocar is of sufficient strength so that it will not bend with the necessary amount of force employed. Its

* Reprinted from *The Laryngoscope*, St. Louis, 1915, xxv, 864.

curve is such that, if the tip of the instrument is placed under the inferior turbinate anteriorly, the handle rotated toward the midline and the force employed directed upward, outward, and backward, the trocar will readily pass into the antrum at the thinnest portion of the lateral wall, about half-way back in the nasal passage. A syringe with catheter tip may be attached to the rubber tubing and the antrum irrigated. If it is necessary to irrigate the antrum in a few days, the irrigating cannula, a Killian cannula bent in the same shape as the trocar, is most useful, since it is a little smaller in diameter and it readily passes into the same opening without the necessity of feeling along the lateral nasal wall to locate it. By this method no local anesthetic is required. These instruments have been used at the Mayo Clinic for the last three years with entire satisfaction.

FIBROLIPOMA OF THE LARYNX*

GORDON B. NEW

After a careful review of literature I have been able to collect reports of only 23 cases of lipoma or fibrolipoma of the larynx. In 1899 Garel¹ presented a case before the Société Française de Laryngologie, and he had at that time collected reports of 13 other cases from literature. In 1901 Garel presented "Une cas d'aversion ventriculaire" before the same society. His patient died of pernicious anemia, and at necropsy the fibrolipoma was found. In 1906 the same author reported another case of a large lipoma of the larynx. He had collected reports of six additional cases by Calémida, De Santi, Goebel, Ingals, Meyjes, and Laurens. In 1909 Goldstein² presented a case of his own with a detailed summary of 11 other cases, and a thorough discussion of the etiology and pathology of the condition. As far as I know these, including the one presented in this paper, make 24 reported cases of lipoma of the larynx.

CASE 133,172.—Mrs. W. C., aged twenty-nine years. Examination June 15, 1915. This patient's previous history was unimportant. She complained chiefly of hoarseness, which had lasted for eight years. She took cold eight years ago, lost her voice entirely for one week, and never fully recovered. A physician had been consulted at the time and had prescribed throat sprays and gargles, but did not make a definite diagnosis. Five years ago a physician was again consulted because of the hoarseness, and she was treated for bronchial trouble. One year ago her larynx was examined, and she was told she had enlarged glands of the neck and catarrh of the head, which was the cause of the hoarseness, and

* Reprinted from Jour. Amer. Med. Assoc., 1916, lxvi, 566-67.

electric massage of the back of the neck was given. Seventeen months ago the patient noted a thickening of the left side of the neck, but it had not increased. While ill with measles three months ago she had spasms of the throat and great difficulty in breathing. When examined, she had slight dyspnea on exertion, but felt perfectly well; there was no cough, no expectoration, no loss of weight. Blood-pressure was 120 and 80. The urine and Wassermann were negative. The nose and throat were negative, except for the laryngeal findings. There was a tumor in the left side of the larynx, covered with normal-looking mucous membrane, apparently bulging the aryteno-epiglottidean fold. The left cord was not visible, and only the posterior third of the right cord could be seen. The tumor did not change its position during respiration. It was quite



Fig. 152.—Tumor, left side of larynx, above true cord, apparently distending the aryteno-epiglottidean fold.

elastic and easily indented with a probe. Its apparent size was one inch in diameter (Fig. 152).

Because of the unusual appearance of the tumor it was thought best to remove it by thyrotomy. The possibility of the condition being an internal diverticulum of the larynx was considered before operating. July 24, 1915, under ether anesthesia, a thyrotomy was done by Dr. Judd. A midline incision was made and the hyoid bone divided to give better exposure of the larynx. On the larynx being opened, a tumor was seen above the left true cord, dilating the aryteno-epiglottidean fold. This was incised, and the tumor, which apparently had no definite pedicle, was readily shelled out. The

patient's voice gradually improved after the operation. She was discharged August 17, 1915, and advised to return in three months for another examination. The excess of tissue on the left side of the larynx following the removal of the tumor prevented full return of the voice, and it seemed possible that the redundant tissue might have to be removed later by the intralaryngeal route. When the patient returned December 2, 1915, her voice was about normal, although a trifle lower in pitch than before the onset of the hoarseness.

Examination showed the larynx normal save for a slight interference in the motion of the left cord and some slight scarring of the left side of the larynx. She stated that her general health had improved markedly since the operation.

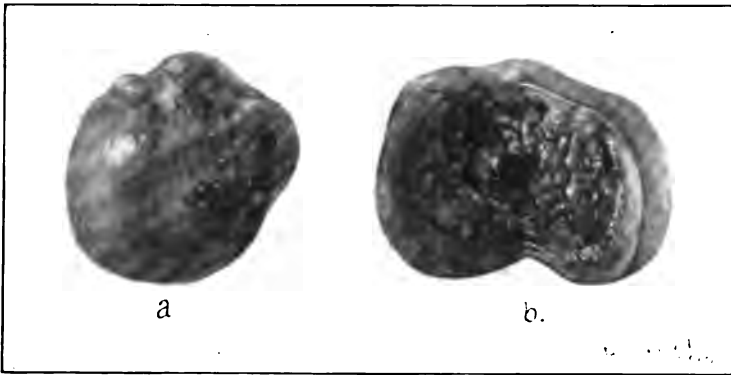


Fig. 153.—Gross specimen, actual size: a, Intact; b, on section.

Pathology.—The gross specimen was a round tumor, 2.5 by 2.5 cm. in size, with a complete capsule, but no demonstrable pedicle. On section the periphery of the tumor was firm, while the central portion was broken down and degenerated. Microscopic sections showed mostly fibrous tissue, with some fat-cells, while toward the central portion of the tumor the lipomatous tissues increased in amount. There were areas of degeneration in the section. **Diagnosis.** Degenerating fibrolipoma (Figs. 153 and 154).

Etiology.—Goldstein states that the etiology of lipoma is questionable, and that it may be due to one of three causes: (1) A simple hyperplasia of encapsulated fat-cells which Chiari has

observed microscopically about the plane of the ventricle; (2) an invagination of mesodermic tissue which develops into lipoma; and (3) a disturbance in the chemistry of cells in which fat is deposited. It would seem that the pathology of these tumors does not differ markedly from the pathology of lipoma or fibrolipoma elsewhere in the body, but their presence in the larynx is unusual. In the case herein reported the fact that the tumor did not have a pedicle, and consequently a poor blood-supply, probably accounts for the central degeneration.

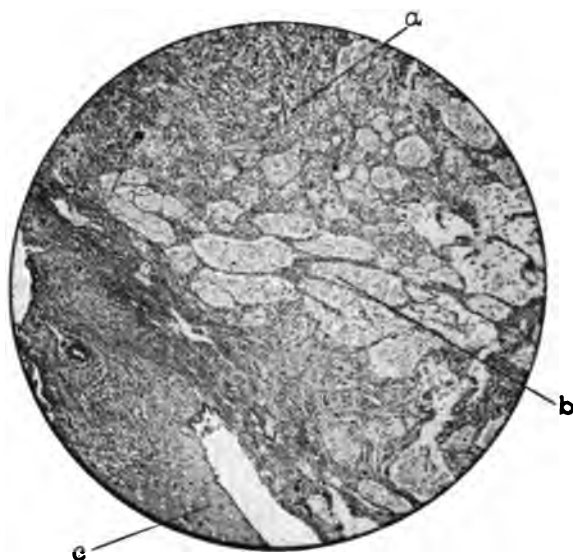


Fig. 154.—Photomicrograph: a, Fibrous tissue; b, lipomatous tissue; c, area of degeneration.

There is no age-incidence in lipoma. The youngest patient reported in the literature was a boy eight years of age (Ingals, 1905). Holt,³ in 1854, reported one in a man of eighty years, as does De Santi, in 1903. The point of origin of lipomas is usually the epiglottis, the aryteno-epiglottidean fold, or the ventricle, and they are usually attached by pedicles which are either quite thin or have thick, heavy bases. On account of its rarity I mention here a case reported by Hunt (1907) of a lipoma attached to the first

three rings of the trachea. The tumor was removed by external operation.

In the case I have reported the lipoma was situated within, and distending the aryteno-epiglottidean fold. It seems to be the only one reported in this position. There was no demonstrable pedicle. The possibility that the tumor originated in the ventricle must be thought of.

Lipomas may be multiple, as in the case reported by Goebel. In this case the tumor was attached to the left aryteno-epiglottidean fold and to the posterior wall of the larynx; one prolongation of the tumor protruded into the mouth like a second tongue, while another portion extended into the esophagus. Golbek,⁴ in 1891, and L. von Schroetter⁵ also have reported multiple lipoma.

Lipomas may also appear as small, pedunculated polypoid tumors. They may be situated so as to fill the entire upper part of the larynx and give rise to marked dyspnea. In some persons dying of suffocation lipoma obstructing the larynx has been found at autopsy.

Diagnosis and Treatment.—In Garel's¹ case a diagnosis of eversion of the ventricle of the larynx was made, and at autopsy the tumor was found to be a fibrolipoma of the ventricle. The picture presented in my patient brought up the possibility of an internal diverticulum of the larynx, the location and elasticity of the tumor indicating similar characteristics to such a condition. It is impossible, however, to make a definite diagnosis of this rare condition until the tumor has been removed and a microscopic examination made.

The small pedunculated lipoma, which can be definitely diagnosed by endoscopic methods, may best be cared for by endoscopic operation. In the large tumors in which it is impossible to make a definite diagnosis before operation it is best to explore by thyrotomy, so that whatever is necessary may be done with less likelihood of danger to the patient. I have seen so few cases of this kind, however, that it is difficult to draw definite conclusions regarding the methods of treatment.

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THE NOSE AND THROAT IN THE ETIOLOGY OF GENERAL DISEASES *

RAY W. PORTEUS

The average physician has been slow to attach the proper degree of importance to the atrium of infection when dealing with local and general diseases. If only the place of origin of a disease in the body can be discovered and eradicated or properly dealt with, the first and most natural and often the most important step in the treatment is accomplished.

Within the last five years the relative importance of the mouth, nose, and throat in the origin of disease has been given a great deal more prominence than in the previous decade. Attention has been called to the fact that infections producing the greatest number of diseases enter the system *via* the alimentary and respiratory tracts: that in these tracts and in the excretory ducts of the body lie the sources of the entrance of organisms which in many instances terminate life. The great importance of the well-known diseases of the nasal passages and their sinuses, the lymphatic tissue of the pharynx, including the tonsils, and the diseases of the gums and teeth has been emphasized. Disease in these regions must be looked upon as a serious menace (Mayo¹).

Let us consider the anatomic basis and the evidence as confirmed by experimental, clinical, and therapeutic results for attaching such importance to these regions. The cavity of the nose, consisting of the two nasal fossæ, is formed by fourteen bones characterized by their irregularity and their participation in cavity forma-

* Read before the Fond du Lac County Medical Society, Fond du Lac, Wis., May 12, 1915. Reprinted from the Wisconsin Medical Journal, 1915, xiv, 191-197.

tions. Five of them contain one or more pockets or sinuses; the sphenoid alone enters into the formation of five cavities and four fossæ. Opening into these various cavities are numerous orifices from other parts of the head. Thus, in either nasal fossa the three meati formed by the turbinates contain seven orifices, all transmitting vessels or nerves or leading into sinuses of the greatest importance. This entire region is richly supplied with blood, has a small amount of musculature, and very little lymphoid tissue.

The pharynx may be described as a conic, musculomembranous bag suspended base up from the basilar process of the occipital bone and extending to the lower border of the larynx, where it becomes continuous with the esophagus. It differs from the nares in possessing more muscular and lymphoid tissue. The presence of this lymphoid tissue has long been noticed and discussed, but its importance has been more particularly emphasized within the last few years.

The most attention has been directed to the part constituting the faucial tonsils. There is a smaller amount of lymphoid tissue in the nasopharynx, which, if hypertrophied, is known as an adenoid. A still smaller amount of lymphoid tissue is at the base of the tongue, in the glosso-epiglottic space, and is called the lingual tonsil. These four structures are sometimes known as Waldeyer's tonsillar ring. As all are of similar microscopic appearance, a description of the larger may be given and by modification applied to each of the others.

Briefly, the faucial tonsil is a lymphoid structure lying between the anterior and posterior pillars of the fauces, consisting of the palatopharyngeus and the palatoglossus muscles, respectively, with the plica tonsillaris above and the plica triangularis below. The inner or median surface is covered by squamous epithelium, while the outer and lateral surfaces are covered by a fibrous capsule of connective tissue. Microscopically, we find finger-like trabeculae of connective tissue extending into the lymphoid substance which serve as supporting structures and carry the blood-vessels and lymphatics. From the median surfaces extend the crypts formed by invaginations of the epithelium and reaching almost to the

capsule. The lymphoid cells of the tonsil are massed together in a loose connective-tissue reticulum, and through this are seen the follicles consisting of germinating lymph-cells and their newly formed lymphocytes. These lymphocytes pass out of the follicles; some of them work through the epithelium into the crypts, while most of them move through lymph-spaces along the trabeculæ and finally enter into the efferent lymphatic vessels. In the crypts are found cast-off epithelium, lymphocytes in divers stages of disintegration, leukocytes, various bacteria, and detritus. When the tonsils are compressed by swallowing, some of the contents is forced out of the crypts and some forced still deeper into them. Here the epithelium consists of one or two layers of cells only; and bacteria can easily gain entrance into the lymphoid tissue. Thus the contents of the crypts, plus heat and moisture, form an ideal incubator for the agents of infection, and from this location invasion through the lymphatics is comparatively easy.

The lymphatics of the tonsil are numerous and arranged as follows: The efferent vessels empty into two main groups: (a) The lymphatic glands near the angle of the lower jaw; then into the superficial cervical chain which drains directly into the inferior deep cervicals; (b) the superior deep cervicals. These glands are 20 to 30 in number, and are located along the internal jugular and subclavian veins. They are divided into a superior and an inferior group; both groups are situated along the internal jugular vein, between the base of the skull and the subclavian veins, and ultimately receive the efferent vessels from all the lymphatic structures of the head and neck. The efferent vessels from the inferior group finally unite to form the jugular lymphatic trunk, which empties on the right side into the right subclavian vein through the right lymphatic duct, and on the left side into the thoracic duct (Deaver²).

Thus the nose and throat form a region studded with cavities and sinuses and containing an abundance of lymphoid tissue: two conditions most favorable for inflammatory processes. Exposed to the inspired and expired air, to contact with food, drink, and other substances taken into the mouth, and with very close and

important relations to the general circulatory and lymphatic systems, the ease and frequency with which the nose and throat become involved in various local and systemic disorders can readily be understood. I will not discuss the ordinary local inflammations, degenerations, or tumors of this region, except as they are concerned in the general or systemic diseases, but rather some of the bacteriologic and experimental evidence which has accumulated to establish more firmly the assertion that the lymphoid tissue of Waldeyer's ring is the most frequent portal of systemic infection.

Wood³ has demonstrated the presence of bacteria in the tonsil of a hog and says: "The anthrax bacillus penetrates through the living, unaltered cryptal but not the surface epithelium. Having gained an entrance, it tends to multiply in the deeper layers and thus passes into the interfollicular tissue. Rapidity of invasion is governed both by the virulence of the bacteria and the susceptibility of the animal. In some sections examined the bacilli were found penetrating the walls of the blood-vessels, and in a few were seen in the blood-current."

MacLachlan⁴ has reported the microscopic examination of 350 pairs of tonsils, and makes the following statement: "We have observed that when symptoms of acute tonsillitis are present there is always a pathologic basis, as shown by ulceration of the lining of the crypts. We therefore feel that a similar lesion is present in the tonsillitis preceding rheumatism, and, as far as we know, this lesion differs in no way from that of acute lacunar tonsillitis. We regard the ulceration of the lining of the crypts as being the vulnerable point of entry of organisms from the mouth. It matters little apparently what bacteria have produced the lesion, for, once the ulcer has formed, it is possible for any type of organism to gain access to the deeper tissues."

Dick and Burmeister⁵ made investigations regarding the toxicity of human tonsils. These were received in sterile gauze, ground in a mortar, and extracts prepared, plated, and examined microscopically. These extracts were injected into rabbits, guinea-pigs, and dogs. Many interesting observations were made regarding

the effect on the injected animals and their condition antemortem and postmortem. Their conclusions are:

1. The extracts of tonsils are acutely toxic for animals.
2. These substances affect animals in a manner similar to that of anaphylactoin.
3. The relation of the toxicity of tonsil extracts to the bacterial flora demands further study. The results of this work, however, would indicate that, as a rule, extracts of those tonsils are most toxic which are associated with hemolytic streptococci.

Davis⁶ made a study of the tonsils in their relation to chronic articular, renal, and cardiac lesions in 113 cases, and his data may be summarized briefly as follows:

Arthritis.—Hemolytic streptococci were found in all of the 28 cases examined and were predominant in 25 cases. Arthritis was promptly produced by the injection of the bacteria into the veins of rabbits.

Nephritis.—Ten cases studied: 9 showed hemolytic streptococci. On injection into the veins of rabbits, all 10 developed lesions of the tendon-sheaths or joints; the kidneys and urine remained negative.

Endocarditis.—Ten cases studied; cultures from 4 of the 6 showing hemolytic streptococci were injected into rabbits, and arthritis promptly developed. Of the remaining cases, 2 gave pure pneumococci and 2 pneumococci mixed with other bacteria. Rabbits were injected with three of the pneumococci strains; 2 developed marked vegetative endocarditis.

Of the remaining cases, nearly all with histories of repeated attacks of tonsillitis, 61 were classified as tonsillar hypertrophy. In 50 the bacteriology showed hemolytic streptococci in almost pure cultures; pneumococci predominated in 2; influenza bacilli in 3. Seven strains of the streptococci were injected into rabbits, all developing arthritis. One case of multiple neuritis without arthritis or heart lesions, and in which the crypts revealed pure hemolytic streptococci, produced a rapidly fatal multiple arthritis in a rabbit. The microscopic examination of the tonsils in this

of Highmore. The lymphatic glands along the superior laryngeal, recurrent laryngeal, and glossopharyngeal nerves become enlarged and swollen; by pressure on these nerves or by involving them in the inflammatory reaction there is a resultant neuralgia or neuritis; disturbed functions, such as hoarseness, loss of voice, cough, difficult deglutition; defects in hearing, dyspepsia, or disturbed heart action. He remarks that "such tonsils may not be, and usually are not, large or acutely inflamed."

7. *Cervical Adenitis*.—Wood,⁹ after some original work on tuberculous absorption through tonsillar tissue, reviewed the literature and summarized the findings of autopsies on persons dying of tuberculosis. In 145 autopsies, 103, or 71 per cent., showed secondary tuberculous changes in the tonsil. In 1671 autopsies there was primary tuberculosis of the faucial tonsil in 88, or more than 5 per cent., and of these, the pharyngeal tonsil was infected in 10 per cent. Various pathologists studied tonsils removed from patients having adenitis, and all agree that diseased lymphoid tissue is the channel of tuberculous infection of the cervical lymph-glands.

8. *Endocarditis, myocarditis, pericarditis, arthritis, nephritis, chorea, osteomyelitis, pleurisy, phlebitis, meningitis*, and various eruptions of the skin may be mentioned. The relationship between tonsillitis and rheumatism, commented on long ago, is now firmly established. Recently many writers have reported cases of relapsing iritis, phlyctenular and interstitial keratitis, etc., which have long resisted the usual lines of treatment, but quickly vanished after the removal of diseased tonsils.

Archibald¹⁰ has made the following observations: (1) The frequency of a previous history of tonsillar disease in rheumatism and chorea; (2) the frequent occurrence of the two diseases together or at different times in the same individual; (3) the liability of the two diseases to be complicated by cardiac affections. He refers to Rosenow's work in rheumatic infection, which proved conclusively that definite strains of the same bacteria have a predilection for special tissues and organs. Following this idea he says: "It would seem probable that chorea also is produced by a strain of strepto-

coccus which has a special tendency to attack the central nervous system." Supporting this theory, he refers to the work of Dick and Rothstein.¹¹ These investigators isolated a streptococcus from the throat of a patient with chorea of five years' duration. Similar organisms were isolated from a number of patients with more acute chorea. A dog injected intravenously with a growth of this streptococcus developed choreic movements within twelve hours. Archibald gives a detailed report of seven patients with chorea who had had tonsillectomies performed within the last three years. Briefly summarized, he found:

1. The patients gave histories either of tonsillitis or inflammatory rheumatism, or of both.
2. All presented choreiform movements at the time of operation.
3. The severity of the symptoms was marked in 5 patients; 6 had very large diseased tonsils; 1 had medium-sized tonsils with crypts.
4. Cardiac complications: 4 had mitral regurgitation; 3 had no cardiac lesion.

When the tonsils were removed from these patients, not only did the general health improve, but the choreic movements ceased in a remarkably short time. In a very few weeks they were in a different condition both mentally and physically.

The recognition of an infected tonsil is often a matter of some difficulty. In making the diagnosis the mucosa of the surface of the tonsil and of the pharynx should be carefully inspected. The presence of redness and of a granular surface with the openings of the crypts containing pus or caseous material will often be noted. The anterior pillar may be retracted, and pressure applied to the base of the tonsil. If the tonsil is diseased, there will be more or less pain, and the patient will flinch from the tenderness of these diseased areas. Caseous materials or droplets of pus frequently exude from the crypts. Such tonsils may or may not be enlarged; if enlarged, they are the more easily recognized. They may vary from a hazelnut to a walnut in size, and may project into the throat, but more often are deep in the tonsillar fossæ.

Shambaugh¹² has emphasized two points in the recognition of such tonsils:

1. *The History of the Case.*—It is usually found that the systemic infection develops simultaneously with or immediately following an acute tonsillitis. In other cases latent foci may be retained in the depths of the tonsil; these may become active at later periods, so it is important to look for a history of tonsillitis, quinsy, sore throat, etc.

2. *The Examination of the Tonsil.*—He especially calls attention to the large flat tonsil with a granular surface. The appearance is due to hypertrophy of the connective tissue, with partial obliteration of the parenchyma. In conclusion, he states that—(a) “Chronic infection in tonsils can often be detected in cases in which there has been no history of acute tonsillitis; (b) chronic infection in the tonsil may be present with no evidence, either from the history or examination; (c) such tonsils should be removed when no other foci of a severe systemic infection can be detected.”

There may be various other foci of infection responsible for systemic disease, though probably the tonsil is the most frequent and the most important. The dentist, the nose and throat specialist, the gynecologist, the gastro-enterologist, etc., may disclose other sources of infection in the examination of difficult or obscure cases. These findings should be correlated for use in treatment by the family physician or internist.

In cited cases tonsil operations have failed to afford the expected improvement. There may be various reasons to account for such failure. Granted that the tonsils were the only foci of infection, all others having been eliminated, and no bodily structures irreparably damaged, by far the most common cause of failure is the incomplete removal of the tonsil. Remnants are left behind, only to be covered by the scar tissue, which more or less closes and seals the remaining crypts. The remnant is thus converted into a most dangerous focus of systemic infection. That such instances are not uncommon is shown by the work of Cocks¹³ in New York, in which he was assisted by Maxwell, of the Department of Education, and Baker, of the Department of Health, in checking up the results

of tonsil operations on public school children. The following are among Cocks' summarized statistics:

(a) Of 89 operated on, 9, or approximately 10 per cent., received mutilations of the soft parts adjoining the tonsils.

(b) Of 21 operated on without general anesthesia, 19, or more than 90 per cent., were badly done.

(c) Of 52 operated on with general anesthesia, 12, or 25 per cent., were poorly done.

(d) If to this number of cases receiving mutilation are added the number badly operated on, both with and without general anesthesia, there will be 26.9 per cent. badly done. In addition, there were 31 children who required further treatment for nasal conditions.

In a minor degree much that has been said regarding the faucial tonsil may be applied to the pharyngeal tonsil or adenoid. The arrangement of this lymphoid structure resembles that of the faucial tonsil, the principal difference being the size. Also, the capsule is absent and the crypts are not so numerous nor so conspicuous. Exposed to the same sources of infection that the tonsils are, except to a less degree, this structure may cause less disturbance because its location permits an unrestricted inflammatory expansion and furnishes better drainage of its excretions. All are familiar with the large adenoid in children, its effect on them, and the truly wonderful improvement in the general physical and mental condition following its removal.

I wish to emphasize the frequency with which large adenoids exist in the adult. Any one may confirm this by the employment of the postnasal mirror as a routine in the examination of patients. Even with no history of mechanical obstruction to respiration, no perceptible interference with deglutition or the sense of hearing, it has frequently been my experience to find large adenoids in the nasopharynx of the adult. Occasionally their surface presents large open crypts from which exudes mucus or a mucopurulent discharge. The significance of this is obvious, and the removal of such adenoids is of marked benefit to the patient.

Matthews¹⁴ has called attention to the pathologic conditions in

the nose, in the accessory nasal sinuses, and the nasopharynx, which are so frequently found in patients having true bronchial asthma. In 184 cases reported 58 had polypi in one or both nostrils and 63 had suppuration of one or both antra. Therapeutically he found almost invariable relief of the asthmatic symptoms to be in direct proportion of the extent of improvement in the pathologic conditions of the nose, sinuses, and nasopharynx. He reviews the experiments in anaphylaxis by Theobald Smith and others, and shows the similarity of this condition to that found during a paroxysm of bronchial asthma. An attack of hay-fever and the asthma that accompanies it have been produced by the injection of a minute quantity of the toxalbumin of the pollen into the person subject to such affections. No reaction occurs in normal individuals. The practical application of these observations is stated as follows:

“It has been found that a foreign proteid capable of sensitizing the individual, and later of producing the anaphylactic shock, may result from autolysis of retained placenta or other tissues. The frequency with which retained and altered mucoid and purulent discharges are found in the nostrils or nasal sinuses suggests that here is the site of the production and entrance into the blood of the foreign proteid which produces the anaphylactic reaction in these cases. The quantity of foreign proteid necessary to sensitize and later to produce the anaphylactic reaction in a susceptible individual is so small that the known absorptive powers of the nasal mucous membrane could undoubtedly pass it into the blood under suitable conditions. Moreover, the reaction has been produced experimentally in guinea-pigs by the inhalation of animal emanations followed by the injection of serum from animals of the same species. The results of treatment of nasal conditions in asthmatic patients present still other analogies to anaphylaxis. Operation to establish free drainage and aëration of the mucous membranes of the nose and accessory sinuses prevent retention of secretions, while in other cases the same may be accomplished by local treatment to stimulate profuse discharge so that secretions are washed away before autolysis occurs. This prevents the formation and

intermittent absorption of the specific foreign proteid which causes the anaphylactic reaction commonly known clinically as asthma."

This theory is being applied practically in our work at the Mayo Clinic with results that are uniformly good and often remarkable.

Bearing in mind the many systemic disorders in which pathologic conditions of the nose and throat are causative or contributory factors, routine physical examinations should always include a thorough inspection of this region. In this way the real nature of many obscure systemic conditions will be revealed with great clearness; and treatment, as indicated by such examinations, will be followed by the most satisfactory results.

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RADIOGRAPHIC DIAGNOSIS OF METASTATIC PULMONARY MALIGNANCY: A REPORT OF 71 POSITIVE CASES *

ALEXANDER B. MOORE

Our object in presenting this paper is twofold: First, to impress on roentgenologists the typical appearance of metastatic malignancy in the lungs; second, to call the attention of surgeons and internists—(a) To the relative frequency of the condition; (b) to the indefinite clinical pictures these cases present; and (c) to the high percentage of correct radiographic diagnoses that can be made. While roentgenologists have long recognized metastatic pulmonary malignancy as a definite radiographic entity, the literature is woefully deficient in any description of their work, and the accuracy of the radiographic examination is unknown to many physicians.

Bristowe,¹ as early as 1860, called attention to the fact that malignant conditions are prone to metastasize in the lungs, and stated that these areas were capable of secondary degeneration and infections, thereby simulating many pulmonary diseases. Warfield² has reported a case of pulmonary metastasis from cancer of the breast on which he performed an autopsy. He gives an interesting review of the literature, and says that while in most textbooks the condition is described as rare, it is in reality far from uncommon, and that at least one-third of all patients dying from cancer of the breast have metastasis in the lungs. He further quotes from the report of cases from the Middlesex Hospital in which metastases were found in the lungs in 178 out of 516 autop-

* Read before the American Roentgen Ray Society, Atlantic City, September 22-25, 1915. Reprinted from the Amer. Jour. Roentgenology, 1916, lii, 126-30.

sies performed on persons who had died from cancer of the breast. In discussing his case Warfield² calls attention to the relatively good general condition of the patient, and emphasizes the indefinite character of the signs and symptoms. He believes that an antemortem diagnosis cannot be made in a large percentage of these cases.



Fig. 155.—(136,890.) Two large areas of metastasis in right lung, secondary to sarcoma of the pelvis.

This report is based on a series of 71 positive cases examined at the Mayo Clinic by both clinical and radiographic methods, and in which the combined findings have been tabulated. The two examinations have been conducted independently, and in a majority of instances the radiographer had no knowledge of either the clinical history or findings until after his report had been presented.

There were 39 women and 32 men in this series. The average age was forty-five and one-half years. The average time since the primary growth was noticed was two years and three months. The distribution of the primary focus was as follows: Breast; thyroid; kidney; soft tissues of the hand, arm, shoulder, leg, and thigh; neck; face; hard palate; adrenal; lung; larynx; esopha-



Fig. 156.—(136,800.) Same as Fig. 155. Roentgenogram made thirty-five days later.

gus; uterus; prostate; testicle; sigmoid, and in abdominal and pelvic masses the exact nature of which could not be determined. In four of these cases the seat of the primary lesion was not discovered. While the most common primary focus was the breast, this being the primary seat of the malignancy in 20 cases, it would seem that malignancies probably have no greater tendency to

form metastases in the lungs from this focus than from foci situated elsewhere. This point, however, is still under investigation.

In the 8 cases in which the primary focus was localized in the thyroid there was clinically a higher degree of dyspnea than in the others. This, of course, is explained by the pressure of the thyroid from above; in but one of these cases was the thyroid of the intrathoracic type. In the cancers of the thyroid it has been practically impossible to determine the duration of the primary malignancy, the enlarged thyroid usually having existed for years.

In 11 cases the primary focus was in the soft tissues of the forearm and shoulder and the leg and thigh. Of these, 10 were sarcoma and 1 epithelioma; only 6 of these showed any enlargement of the axillary or inguinal glands.

Of the 5 cases in which there was metastasis from the kidney, 3 had been operated on and 2 showed large renal masses with a definite unilateral hematuria; in 1 the tumor was demonstrated by the pyelogram. Of the cases operated on, 2 were "hypernephroma" and 1 carcinoma.

In 5 of the cases the primary focus originated in the soft tissues of the neck and face; 3 were sarcoma and 2 epithelioma (1 lip and 1 cheek). According to the literature, it seems quite unusual for malignant lesions above the clavicle to metastasize into the trunk. Our experience tends to confirm this, since these 5 cases form a very small percentage of the total number examined; however, the primary lesions were not nearly so extensive as in many cases that did not show metastases.

The 2 cases originating in the uterus were both cancers—one from a small lesion of short duration in the cervix, without enlarged glands. The uterus was freely movable, and the patient apparently in splendid condition. The other was secondary to a degenerated myoma that had been removed six months before. This latter case was complicated by a pleural effusion and the patient was in *extremis*.

In 2 of the cases the origin was in the esophagus. Neither presented any unusual radiographic features; extreme prostration,

due to their inability to take food, was the most marked clinical characteristic.

The primary focus was in the prostate in 2 cases and in the testicle in 2. The 2 in the prostate were carcinoma and 1 had metastasized in the pelvic bones. Those originating in the testes were sarcoma; both had been operated on and neither had any local recurrence.

There was 1 case originating in the hard palate, 1 in the larynx, 1 in the adrenal, and 1 in the sigmoid; all these were carcinomas presenting no unusual features.

One case, apparently both from clinical and roentgenologic standpoints, originated in the lung. The clinical history and findings as to the primary growth were very definite, and the radiologic evidence of the metastases was beyond question.

In 59 of the series we were able to obtain pathologic reports as to the nature of the growth. Many patients brought reports from other laboratories, and in others either a gland or a piece of tissue from the primary growth was removed for microscopic examination. These specimens were classified pathologically as 40 carcinomas, 16 sarcomas, and 3 "hypernephromas." Seven autopsies were performed in this series of cases, 4 in our laboratories and 3 elsewhere. The small percentage of autopsies is explained by the fact that most of the patients remained in the clinic but a few days, and while in many instances the family physician was requested to obtain permission for an autopsy, very few were performed.

Glandular Enlargement.—Thirty-five of these patients showed some palpable enlargement of the superficial glands, and 8 showed enlargement of the deep glands.

Extent of Primary Growth.—Apparently no idea as to the presence of pulmonary metastasis can be gained from the extent of the primary growth. Many cases with extensive involvement showed no metastasis, while in many of the cases included in this report the primary growth was small and clearly operable, except for the radiologic evidence of metastasis.

Other Foci of Metastasis.—Fourteen of these cases showed

metastasis in organs other than the lungs or lymph-nodes. The other organs most frequently involved were the liver, bones, and brain.

Patients Operated On.—Forty-two of these patients had been subjected to surgical procedure for the removal of the primary growth; of these, 19 showed local recurrence. The average time from the operation to the discovery of the metastases was fifteen months.

Symptoms.—Cough was the symptom noted most often, being present in 32 of the 71 cases. The character of the cough was usually dry hacking, and in many cases was little more than would be expected in patients of the cancer-age. It was usually unproductive, expectoration having been noted in but 8 of these cases. Hemoptysis was rare, but 4 of these patients giving any history of blood-spitting. The so-called prune-juice sputum, regarded by some observers as indicative of this condition, was noted in none of our cases.

Dyspnea.—The next symptom in order of frequency was dyspnea; this occurred in 30 of our cases. The dyspnea was usually progressive, and, when marked, tended to be spasmodic in character, quite often simulating asthma.

Pain.—Pain referred to the thorax was noted in 14 instances. This pain was usually described by the patient as a gnawing one, and was not influenced by respiration.

Temperature.—But 4 of these patients showed an increase in temperature at any time, and none of them gave a history of night-sweats.

Fluid.—There was both clinical and radiographic evidence of pleural effusion in 12 of the cases, and in 10 the effusion was tinged with blood when aspirated.

Physical Findings.—A very striking feature was the relative absence of definite physical findings. But 16 of the patients presented signs that could be construed as indicative of pulmonary metastasis; of these 16, 12, as mentioned above, had pleuritic effusions.

Loss of Weight.—Loss of weight was not marked; in fact, the

most striking feature in reviewing this series was the relatively good condition and fairly healthy appearance of most of the patients, save for the anemia, which was no more marked than in any other patient suffering from a malignant lesion.

If the above tabulation can be regarded as indicative, the clinical picture of pulmonary metastasis is, indeed, an indefinite one,



Fig. 157.—(81,323.) Two small malignant nodules in the upper right lobe, secondary to carcinoma of the breast.

the most common symptom—cough—being present in less than 50 per cent. of the cases. No idea as to their existence can be obtained from the extent of the primary lesion or the presence or absence of glandular involvement. Only by routine radiographic examination in cases of malignancy will the diagnosis be made in the majority of these cases.

Radiologic Appearance.—In the radiologic examination of the thorax in suspected cases of metastatic pulmonary malignancy, as in all cases examined where a study of the intrathoracic viscera is desired, the plates should be made and studied stereoscopically, and great care and conservatism should be exercised in following



Fig. 158.—(109,789.) Extensive areas of metastasis in both lungs, secondary to an abdominal carcinoma, probably primary in the stomach.

out details of the examination. In our work the plates have been made routinely by the stereoscopic method, the patient, in the upright posture, facing the plate, the tube shifted parallel to the spine. If necessary, a second pair with the back to the plate may be made. Some have been studied by the fluoroscope as well, but only in

those cases complicated by pleural involvement has any additional information been obtained by this means.

The radiologic appearance of metastatic malignancy is quite typical, and consists in the localization of clear-cut, circumscribed areas of increased density, varying in size, in our experience, from the head of a small hat-pin to that of an orange. Their density varies from a faint shading to a degree approximately equal to that of the heart, depending on the stage of the disease. These areas are usually multiple, are found near the hilus, and are situated nearer the base than the apices of the pulmonary lobes. Radiographically, they may be differentiated from inflammatory areas of increased density by the clear-cut line of demarcation that separates them from the surrounding tissues, in sharp contrast to the so-called "fimbriated halo" found in inflammatory conditions. No idea as to cellular structure can be obtained from the radiograph, all forms of malignant tumors apparently giving the same appearance in the radiograph.

Differential Diagnosis.—Radiographically, the conditions that must be differentiated most often from metastasis are tuberculosis, syphilis, and cysts, particularly hydatids. Tuberculosis can usually be excluded by the lack of any clear-cut line of separation from the surrounding parts, by the mottling that is so well known to us all, by the smaller size of the areas of increased density, and by their tendency to cavitation.

Syphilis.—Syphilis, according to Virchow,³ occurs in the lungs in two forms: namely, interstitial infiltration and gumma. He states emphatically that coarse gumma is never seen without a surrounding infiltration. Rothschild⁴ states that syphilis is shown in the radiograph as a diffuse shadow; this should be a distinguishing feature in the radiograph. However, we have seen no proved cases of pulmonary gumma, nor do our records of nearly 2,000 autopsies show any. Most observers agree that syphilis in the lungs is very rare. Osler⁵ reports but 12 cases out of 2500 autopsies. The Massachusetts General Hospital reports no cases in 3000 autopsies. In our cases the possibility of syphilis was always excluded by the Wassermann test.

Cysts.—Cysts may usually be differentiated by their greater size and density. A large percentage of cysts of the lung are hydatids, and are usually located in the right lower lobe; most of them are secondary to cysts of the liver and gain entrance to the lungs by penetrating the diaphragm.

Radiographically, 60 of our 71 cases showed multiple nodules



Fig. 159.—(96,087.) Multiple areas of metastasis in both lungs, secondary to carcinoma of cervix.

and 11 showed single nodules. One of the most striking radiographic features was the relative absence of any increase in the mediastinal shadow, only 27 showing any increase at all over the normal. This would tend to confirm the observation that these metastases are embolic and travel through the blood rather than the lymph-stream.

A positive radiographic diagnosis of metastatic pulmonary malignancy was made in 58 of our series, in 12 a slightly modified report, and in 1 case a negative report. In this latter case, through an error in interpretation, the nodule was not discovered until a second examination was made.

CONCLUSIONS

From the above study the following conclusions may be drawn:

1. Pulmonary metastatic malignancy is not an uncommon condition, and may occur regardless of the seat of primary focus.
2. Pulmonary metastasis bears no relationship to the extent or duration of the primary focus.
3. The clinical picture, in a majority of these cases, is very indefinite, neither the subjective nor the objective manifestations being characteristic of the condition.
4. Metastatic pulmonary malignancy is a definite radiographic entity, appearing in the roentgenogram as clear-cut, circumscribed areas of increased density.
5. In many instances the diagnosis can be established only by the radiograph. By routine radiographic examination of the thorax many patients suffering from malignancy will be saved from useless and unwarranted surgery.

LOCATION OF PRIMARY FOCUS IN CASES SHOWING RADIOGRAPHIC EVIDENCE OF METASTASES IN THE LUNGS

	CASES
Breast	20
Thyroid	8
Kidney	5
Soft tissues of forearm and shoulder	6
Soft tissues of leg and thigh	6
Soft tissues of neck and face	5
Uterus	2
Esophagus	2
Prostate	2
Testicle	2
Hard palate	1
Larynx	1
Sigmoid	1
Adrenal	1
Lung	1
Abdominal and pelvic masses	4
Origin not determined	4

DIAGNOSIS OF METASTATIC PULMONARY MALIGNANCY 617

Men.....	32
Women.....	39
	YEARS
Average age.....	45.5
Average time since growth was noted.....	2¼
	CASES
Histologic examination.....	59
Carcinomas.....	40
Sarcomas.....	16
Hypernephromas.....	3
Enlargement of superficial glands.....	35
Enlargement of deep glands.....	8
Other foci of metastasis.....	14

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THE TREATMENT OF CHRONIC NON-TUBERCULOUS EMPYEMA*

SAMUEL ROBINSON

Certain thoracic diseases which for generations have fallen to the lot of the surgeon are yet badly handled. Conspicuous among these is that patriarch of the surgical scrap-heap, chronic empyema. There is obvious opportunity for improvement in the treatment of this disease.

A patient thus afflicted presents a typical picture: that of a stooping, one-sided, emaciated, pale, club-fingered person—not seriously ill, but nevertheless a chronic invalid. He oscillates daily between the surgical dresser's room and the park bench, his family meanwhile suffering the poverty incident to his inefficiency. There is generally an opening somewhere in his chest. It has been there for from six months to twenty-five years. He is the survivor of one and perhaps of several operations, and yet pus continues to discharge from his side. The surgeon passing through the dispensary recognizes one of these unfortunates and proverbially remarks to himself, "Some day when there is a shortage of more interesting material I must take out some more of that man's ribs." The patient meanwhile continues the object of procrastination and neglect.

It may be said that the chronicity of these cases is rather more the result of the surgeon's lack of persistence in bringing his patient to the point of cure, than it is to ill choice of method or lack of surgical skill.

LOCALIZATION OF CAVITY

Assuming that the diagnosis of chronic empyema has been made, the first step in treatment is the determination of the size

* Missouri Valley Med. Soc., September 23, 1915, Des Moines. Reprinted from Surg., Gyn. and Obst., 1916, xxii.

and location of the persisting cavity. This, of course, depends upon the direction and extent of lung retraction. Auscultation and percussion as a means of diagnosis are valueless, or, to say the least, so inadequate compared to other methods at our disposal that they may be disregarded.

If a sinus in the wall of the chest has been produced *per necessitatem* or by previous operation, an olive-tipped flexible probe, if inserted into the cavity, will at least disclose the longest diameter. If rotated within the cavity, the arc expressed by the olive tip may be noted from the corresponding rotation of the flattened handle. Thus the lateral diameters may be estimated with surprising accuracy.

Stereoscopic roentgenograms contribute in the localization of a cavity according to circumstances. If the empyema is of long duration and has never been drained, the roentgen ray will cast a deep shadow which is continuous with and not distinguishable from the adjacent thickened pleura. The actual size and location of a cavity is, therefore, not demonstrated. If the pleural pus has been draining through a bronchus, pyopneumothorax is present; a fluid level is shown. The empty part of the cavity is outlined, and the shape of the remainder may be roughly estimated. If the cavity has been drained through the chest-wall and is practically emptied of its contents, the stereoscopic roentgenograms will portray the outlines of the cavity in a large proportion of cases. The exceptions are those instances in which the cavity is not situated in the usual lateral portion of the chest (Figs. 160 and 161), but rather anteriorly or posteriorly (Figs. 164 and 165). Under such conditions the lung is not thrown in silhouette, as in cases in which there is a lateral cavity, but rather overlies the cavity, and its own markings obscure the cavity outlines. It would seem that the stereoscope would overcome this obstacle, but unfortunately such is rarely the case.

By far the most accurate and satisfactory method of outlining cavities associated with a sinus of the chest-wall is the following: A narrow bandage or tape is unwound and immersed in barium sulphate and water mixed to the consistency of thin cream. With

a probe it is fed through the sinus into the cavity, care being taken that each loop of the tape is carried to the limits of the space until it is packed full. A stereoscopic radiogram is then taken (Figs. 168 and 169). The mass of barium-soaked tape casts a definite shadow which is distinguishable from the lung-shadow, even when the two

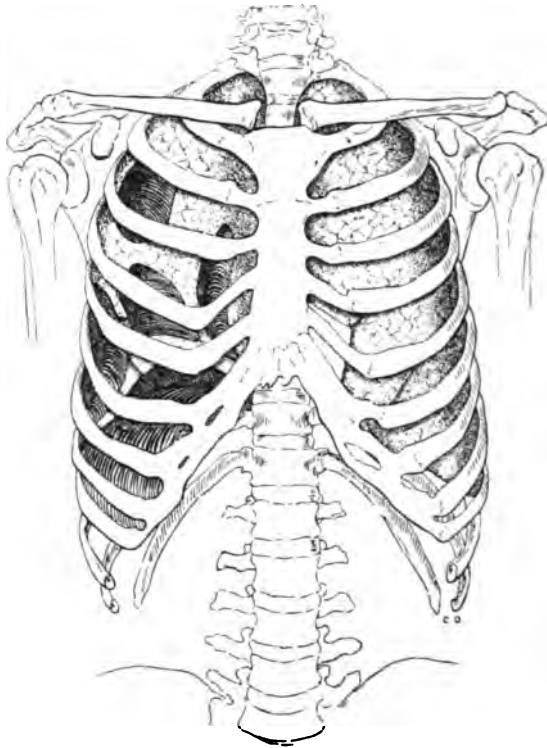


Fig. 160.—Diagram. Small lateral empyema cavity. The common type: generally demonstrable in radiogram. Curable by shrinkage type of operation, or by any of the cavity filling operations. Decortication not necessary.

are superposed, as in the anterior and posterior cavities mentioned above.

The injection of liquid mixtures containing bismuth or barium has long been utilized in conjunction with the roentgen ray to demonstrate empyema cavities. It is often difficult to completely

fill the cavity with such mixtures. If a bronchial fistula is present, a sudden flooding of the trachea may occur, the consequences of which are rarely fatal, but sometimes alarming. Bismuth retained after such infections, particularly when the sinus is small and the outflow is obstructed, may lead to a moderately severe reaction;

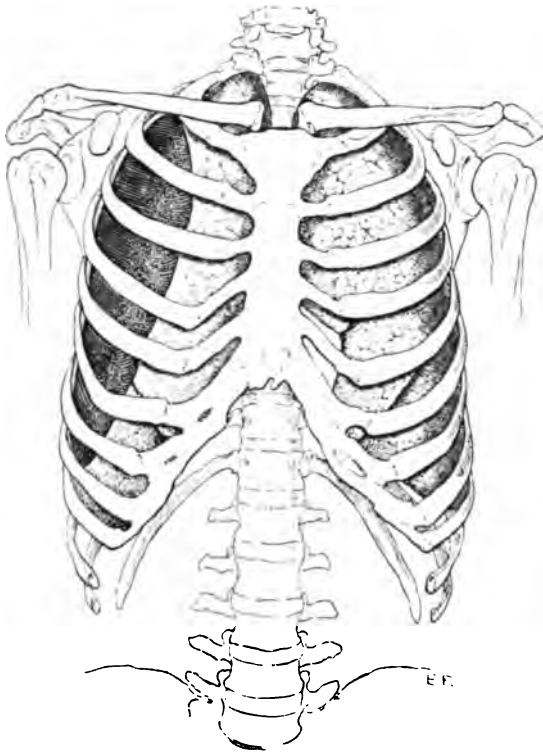


Fig. 161.—Diagram. Large lateral empyema cavity. A type demonstrable in radiogram. Suitable for decortication, followed by further osteoplastic resections of either the filling or shrinkage type.

this is an unwelcome incident in the course of a purely diagnostic measure. Suffice it to say that the packing with barium-soaked tape is simpler, safer, and equally efficient in demonstrating cavities.

The cystoscope has been employed to survey empyema cavities. There is little to be derived therefrom.

The diagrammatic drawings shown in Figs. 160-166, were made from a skeleton thorax in which the retracted lung was modeled in wax in many of the positions in which the writer has found it at operation. To these might be added illustrations of the many types of smaller cavities resulting from local-



Fig. 162.—Diagram. Lateral view of cavity shown in Fig. 161. Illustrates the enormity of any osteoplastic resection undertaken previous to an attempt at decortication.

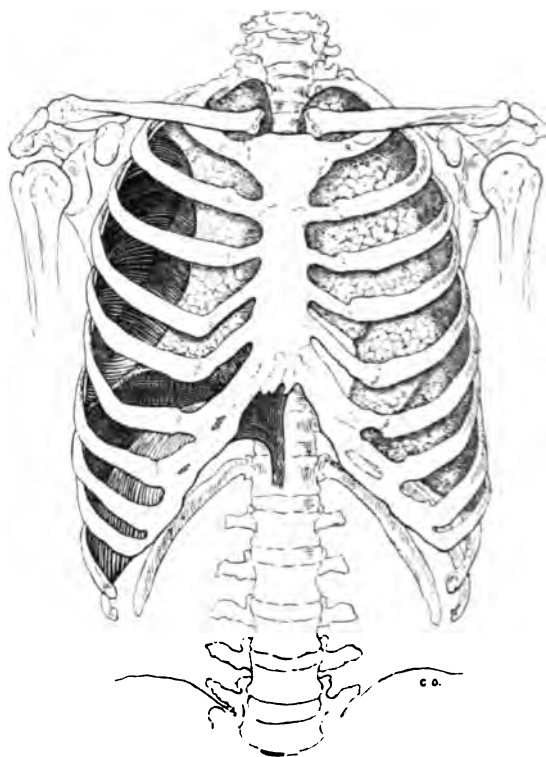


Fig. 163.—Diagram. Type of chronic empyema cavity which may follow pneumonia of the upper lobe. External filling type of operation indicated.

ized septic effusions, including the particularly rare form of interlobar empyema.

PRELIMINARY DRAINAGE

It is plainly apparent that no one method of treatment nor any one type of operation would be suitable for all chronic empyema

cavities, which assume such a diversity of size, shape, and location. Nevertheless, one cardinal rule of treatment may be laid down at the outset which is applicable to them all. No operation designed for the obliteration of a chronic empyema cavity should be performed until this cavity has been provided with wide-open drainage at the lowest possible point for a period of at least six weeks.

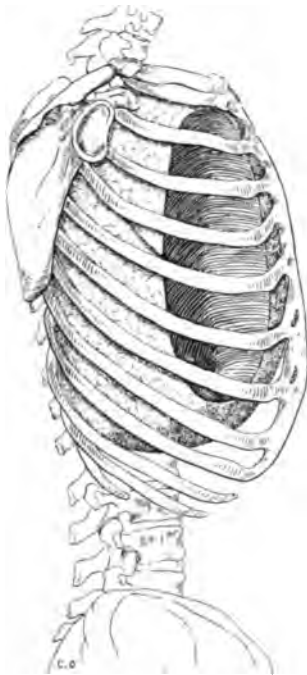


Fig. 164.—Diagram. Anterior cavity. Not demonstrable by radiogram except in lateral view or in conjunction with barium-soaked bandage pack. Suitable type for Schede osteoplasty combined with muscle implantation. Also suitable for the infolding lateral flap operation.

The case to be treated presents one of the following conditions:

1. An incarcerated accumulation of pleural pus which has remained unrecognized and undrained for months and even years.
2. A cavity which “leaks” but does not empty through a bronchial opening, situated generally at a level far above the bottom of the space.

3. A cavity which leaks an absurdly small proportion of its contents through an empyema necessitates opening the chest-wall.

4. A cavity which drains profusely and yet incompletely through an operative wound from which the drainage-tube has been prematurely removed.

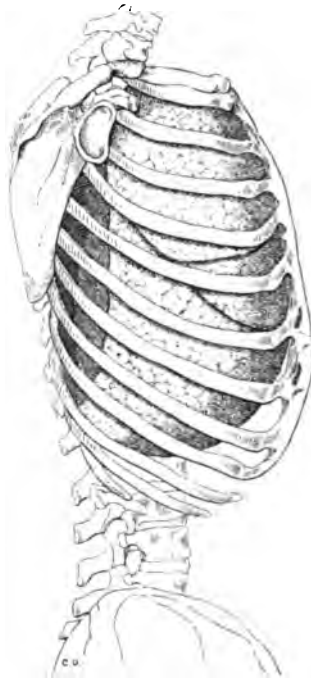


Fig. 165.—Diagram. Posterior cavity. Particularly suitable for the lateral flap infolding operation.

In each and all of these conditions the patient is the unfortunate carrier of from a half-pint to three quarts of residual pus. He is suffering from a chronic, low-grade septic absorption. He is a poor surgical risk, particularly for the type of operation to which he must eventually be subjected.

A preliminary drainage operation is, therefore, indicated in nine-tenths of the cases first met in a surgical clinic. The bottom of

the cavity is located with an exploratory needle attached to a tight glass-barreled syringe. It matters little whether or not there are already openings in the chest; generally they are too high and too small to be regarded. Through such openings a curved probe

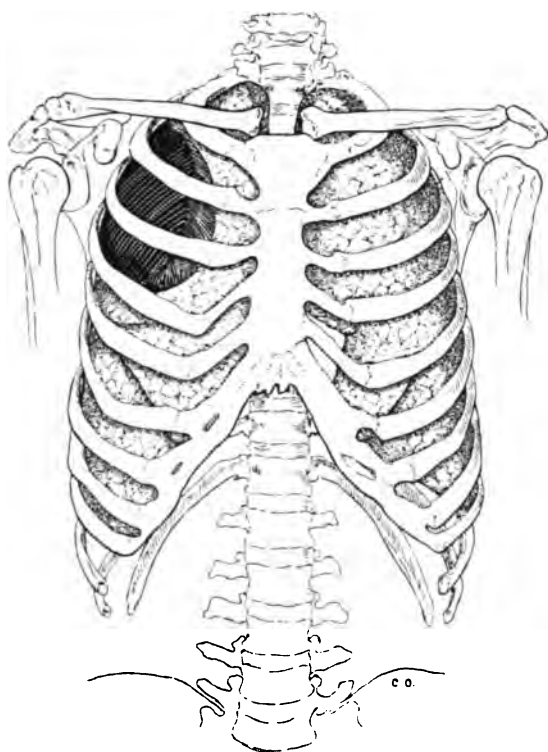


Fig. 166.—Diagram. Multiple encapsulated empyema cavities. Generally fatal in the subacute stage because of impossibility of diagnosis and localization. Drainage operation evacuates one cavity only.

may aid in locating the real bottom of the pleural space, at which point an inch of rib is resected and a large tube inserted.

The improvement of a patient thus provided with new drainage is striking. There may be a weight increase of 20 pounds in six weeks. Then and not until then is radical operation to be undertaken.

TREATMENT WITHOUT OPERATION

This subject is scarcely worthy of discussion. Generally speaking, non-operative treatments in chronic empyema are attended with cure only in those patients who would have recovered eventu-

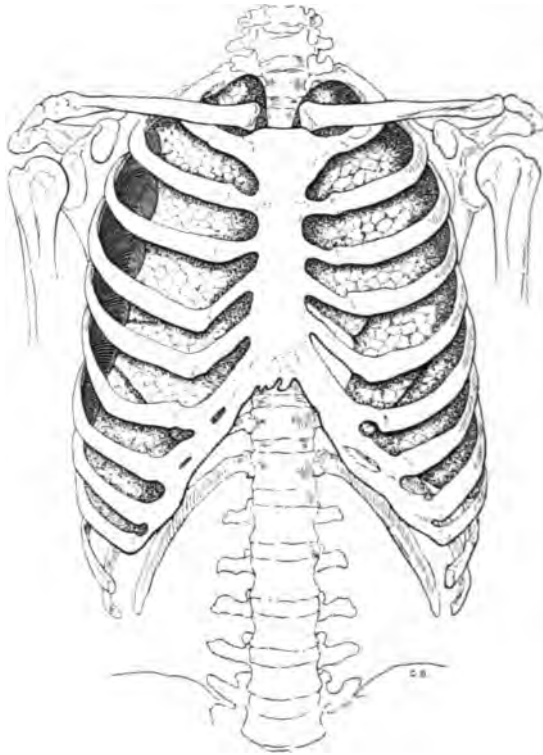


Fig. 167.—Diagram. Combined lateral and diaphragmatic empyema cavities not connecting. Accurate diagnosis generally impossible. One cavity generally drained; the other overlooked. Particularly adapted to operation of Lilienthal type.

ally and with like promptness without any treatment. It is an established fact that fibrous connective-tissue formation on the pleural surfaces occurs with slow but regular growth, diminishing the capacity of the cavity accordingly. Shrinkage of all tissues associated with some deformity further contributes to the obliteration of the pleural space. It is not surprising, perhaps, that the

enthusiastic physician, employing some non-operative method, credits the apparent improvement to his therapy rather than to the physiologic processes which have meanwhile been at work.

Thus the vaccine enthusiast receives his regular pittance for months. His conscience is relieved by the apparent diminution in the amount of discharge. The patient is temporarily encouraged, and he notes further that the discharge is less offensive. From these facts both assume that the cavity is much reduced in size. Vaccine therapy is indicated for symptomatic relief. It will not cure. There is no real evidence that any of the physiologic healing of processes in the pleural cavity are fostered or stimulated by vaccines. The subject is worthy of mention only in the sense of caution. Vaccine therapy has done far more to postpone unnecessarily the obviously necessary surgical procedure than it has ever done, even in the relief of symptoms.

Bismuth and vaselin (Beck's paste) is commonly used as an injection. This form of therapy has definite limitations, which were lamentably overlooked until a number of disasters emphasized them. The mixture has a definite bactericidal action upon the secretions of septic cavities. When an empyema cavity has thus been rendered sterile, the tendency of the chest-wall opening is to close. The cavity remains. Both physician and patient rejoice at a cure which is far more apparent than real. If the outflow of the infected mixture has been incomplete during the treatments, the bismuth incarcerated in the large cavity may gradually produce symptoms of bismuth poisoning. Fatalities unquestionably have resulted. Furthermore, months or even years after the closure of the sinus and the apparent cure of the patient febrile symptoms have developed, with all the other indications of retained infection within the chest. If drainage is not reëstablished, an empyema necessitatis may develop in the scar, to the surprise and mortification of the physician, who finds, on further examination, that a large cavity still persists, which, though temporarily sterilized by the mixture, has, through blood or lymphatics, become reinfected, with dire results.

Empyema cavities of more than six or seven ounces capacity

should not be injected with bismuth and vaselin, except to reduce an overabundant secretion by lowering the toxicity of the infection. In such usage care should be taken that the mixture injected is provided with free, unobstructed escape.

Small empyema cavities, either primarily small or rendered so by previous operations, may be injected with the deliberate intent to sterilize them and to heal their drainage openings. The physician should acquaint his patient with the fact that the apparent cure resulting may not be a permanent one, advising him further that, on the appearance of any untoward symptoms, he should return for consultation and perhaps for reopening of the sinus. Certain observers have been sufficiently cautious in employing this therapy to aspirate with a needle the persisting closed cavity from time to time, to determine the degree of obliteration and the endurance of the sterilization.

The non-operative treatments of chronic empyema, then, some of which have been mentioned in the foregoing, must be employed with caution and with understanding as to the occasions when they are indicated.

SURGICAL TREATMENT

The necessity of preliminary drainage at the extreme bottom of all empyema cavities previous to more radical procedures for obliteration has been emphasized. The patient returns six weeks or two months after this drainage with his maximum resistance. An operative fatality is now inexcusable. It occurs for definite avoidable reasons:

1. When an attempt is made to accomplish the obliteration of a large cavity in a one-stage operation.
2. When there is an erroneous conception of the degree of resistance possessed by a given patient, together with an operative procedure which overtakes his resistance.
3. When the atrocious custom is employed of operating on these patients until symptoms of shock appear; with ignorance of the fact that the maximum shock after such osteoplastic operations is not demonstrated until after two hours.

4. When there is undue regard for hemostasis, loss of blood being far more contributory to shock in such cases than trauma.
5. When there is an excessive expenditure of time.
6. When the administration of the anesthetic is unskilful.

The operations may be discussed as being of two types, each designed to further one of the two physiologic healing processes,



Fig. 168.—Radiogram of empyema cavity packed with barium-soaked tape, showing that a tortuous narrow cavity may be thus packed. Illustrates type of cavity suitable for antiseptic injections (Beck's paste).

namely, shrinking of the diseased half of the thorax, or actual filling of the empyema cavity itself. Any attempts to fill the cavity are necessarily accompanied by a certain degree of shrinkage because of the rib resection necessary to permit accessibility to the cavity. Operations designed for shrinkage, however, may not contribute in the least to actual filling. For example, the Wilms opera-

tion consists in the resection of one-half-inch segments of several ribs at their angles posteriorly, and at the costochondral juncture anteriorly. The normal curve of each rib from angle to cartilage remains unaltered. Approximation of the shafts of the ribs is promoted, nevertheless, by the release of their anchorage front and back. A moderate degree of slumping of the costal arch at the sternal and vertebral ends may also occur. In other words, by this



Fig. 169.—Cavity, incompletely demonstrable by radiogram alone, defined by barium-soaked pack.

type of operation the lateral thoracic diameter is reduced. The lateral contour is considerably flattened, but one fails to produce any actual caving in over the cavity area which could be said to contribute to its filling.

The Estlander operation consists in the excision of several segments of several ribs in any portion of their shafts. A moderate degree of local slumping of the thoracic wall may occur after the

more radical operation of the Estlander type, although its function is essentially to produce a uniform shrinkage. In fact, it was the failure of Estlander's operation to contribute to any marked degree to the obliteration of a cavity which led Schede to describe his operation, the very nature of which accomplishes a local chest-wall collapse. Estlander's name is commonly attached erroneously to operations of the Schede type. One effects shrinkage alone, the other both shrinkage and collapse.

The distinctive features of the Schede operation is the complete removal of the bony wall of the empyema cavity; in other words, the free resection of all ribs overlying the cavity, regardless of the number or extent (Fig. 171). Schede also recommends the removal of the thickened parietal pleura lying beneath the resected ribs, and forming the outer lining of the cavity (Fig. 172). He thus sacrifices a layer of tissue often more than an inch in thickness, increasing one diameter of the cavity correspondingly. He argues that the removal of this leathery, unyielding layer permits more slumping of the skin and muscle-flap into the depths of the cavity, thus gaining more in the obliteration of the space than was lost by the sacrifice of the connective-tissue mass which nature had labored perhaps for several years to produce. He adds that the muscle-surface now forming the outer wall of the cavity will granulate rapidly and aid further in the filling function.

Even the Schede operation, radical and mutilating as it may seem, often fails to accomplish its primary purpose, namely, to produce filling by local slumping. Probably a Schede type of operation was never performed without a certain degree of reduction in the cubical contents of a cavity. This, however, may be explained more by the general thoracic shrinkage which such an extensive rib resection obviously permits, than by local filling. These are two explanations for this "filling defect" (to borrow a roentgenologic term). If the skin and muscle-flap are sutured accurately to their original position, a tense, somewhat tightly drawn covering is provided to the cavity, which spans the space but does not enter it. If, thanks to the paucity of ribs, the skin and

muscle-flap at first spread loosely over the gap, the healing contractions tighten it later into a spanning membrane.

Another explanation of the frequent failure of the Schede flap to assume the concave curve of the cavity is to be found in the error of dividing the covering ribs in such manner that their ends directly overlie the borders of the empyema gap. A rigid bony rim is thus provided to the cavity, over which the flap must make an abrupt pitch in order to follow its curve. If, on the contrary, the ribs are divided an inch beyond the pleural limits of the cavity, the pitch is a more gradual one.

The Fowler-Delorme operation of decortication is designed to fill the empyema cavity from within; the Schede type seeks to fill from without. The Fowler operation, theoretically at least, aims to obliterate chronic empyema cavities in the ideal fashion. It not only should minimize deformity of the contour of the chest-wall, but also, by ridding the lung of its thick pleural covering, favor its reëxpansion, thus restoring more nearly its full respiratory function. All other osteoplastic operations for this disease deliberately abandon the lung itself to its retracted state and to its impaired function. The technic is not elaborate or difficult of execution. Several inches of several ribs in the region of the cavity are resected. Some parietal pleura is removed, producing an opening through which instruments and fingers may strip the visceral pleura from that portion of the lung forming the inner wall of the cavity. Thus liberated, the lung should expand. When it does, the picture is awe-inspiring. The cavity appears to be filled from the bottom up.

Ransohoff's operation is a modification of the decortication type. The visceral pleura is not stripped, but incised with multiple cuts which are intended to reduce the tenacity of the fibrous pleural layer, so that it yields to the ever-present tendency of the lung to expand.

Appealing as the operation of the Fowler-Delorme type may at first appear, the results are not infrequently disappointing. The area of cleavage below the visceral pleura is not always unobstructed. Fibrous bands may cross from the thickened pleura to

the interalveolar connective tissue of the lung parenchyma. In freeing these, lung tissue may be lacerated, causing bleeding and multiple minute air-fistulæ. Hemorrhage may necessitate the termination of the operation before the completion of the decortication; the degree of cavity filling is thus disappointingly minimized. Lung infection has resulted from the laceration of the peripheral air-spaces. Fatalities have occurred from each of these complications.

If, on the contrary, the decortication is readily executed, and the lung, during a forced expiration of light anesthesia, appears to occupy the pleural space, the new relations are difficult to maintain. The lung may be temporarily inflated and forced even to approximation with the chest-wall, but in the presence of an open chest neither negative pressure nor pleural capillarity is present to retain the expansion. To reproduce the normal suction effect of the chest-wall one must close hermetically the operative wound. By so doing one must also imprison infection within the diseased pleural cavity, and local accumulations of pus are dangerously likely to occur. Efforts have been made to suture the inflated lung to the parietes, but, unfortunately, one secures apposition of suture lines rather than of surfaces. Pocketing of infection is again imminent. Positive pressure breathing exercises are religiously carried out during convalescence to maintain inflation, but agglutination between the intermittently opposed surfaces does not willingly occur. The fibrous parietal pleura presents a slimy surface, to which even the freshened surface of the lung may not adhere. The authors of the operation emphasized the necessity of removing both the visceral and parietal pleuræ in order that two raw surfaces might be brought in apposition. Surgeons of late years have rarely attempted the stripping of the parietal pleura. It prolongs an already severe operation and is generally omitted.

Decortication, then, though in given instances of unquestionable value, has its limitations. It contributes to the cavity filling a greater or less degree; it rarely obliterates it.

Inadequate as the osteoplastic resections and the decortications may sometimes appear, it must be admitted that what we



Fig. 172.—Muscle implantation operation. Third step: Thickened parietal pleura in process of removal.



Fig. 173.—Muscle implantation. Fourth step: Latissimus muscle has been split; one-half has been dissected from V-shaped flap and sutured into top of cavity; the remaining half is to be implanted likewise. Note important lateral sutures to muscle to relieve tension upon stitch at top of flap.

of the fibrous pleura is far too meager to assume completely the nourishment of isolated tissue. If, however, muscle is swung into an empyema cavity as a pedicled flap, preserving its original blood supply, it can be relied upon as an efficient filling agent.

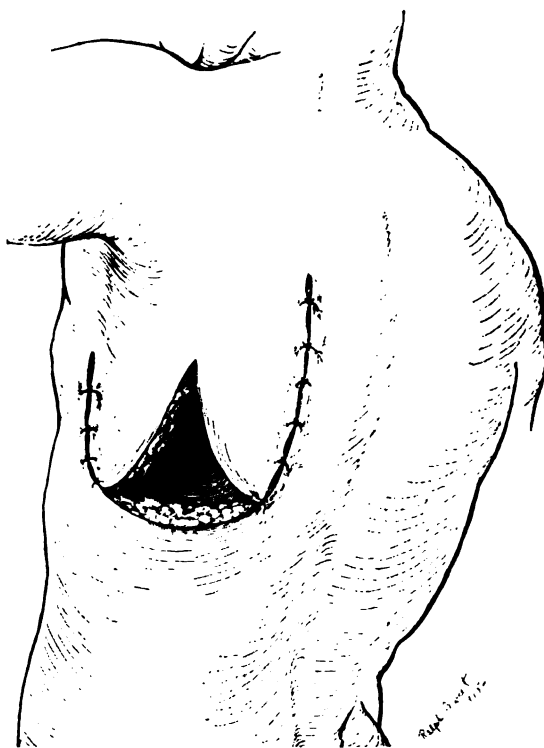


Fig. 174.—Muscle implantation. Fifth step: U-shaped skin and fat flap has been restored. Triangular piece has been excised from border of flap to permit of free drainage, packing, and stimulation of muscle granulations.

Schulten, Sudeck, Ringel, Körte, and Hellstrom have described operations which include the removal of portions of the scapula. In association with this they have utilized the remaining scapular muscles to aid in the filling of the empyema cavity. The excision of portions of the scapula is inadvisable for two reasons: Cavities

can be obliterated without it: and with it associated marked limitations in the movements of the shoulder-joint.

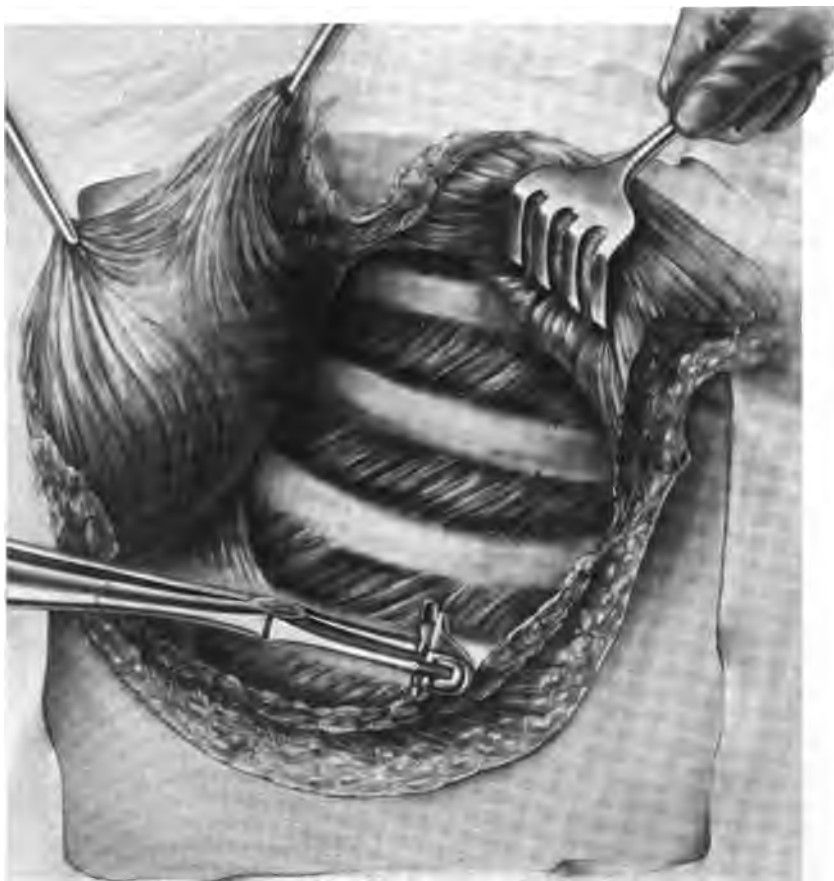


Fig. 175.—Operation for obliteration of a chronic empyema cavity by the infolding of two lateral flaps produced by an inverted T-shaped incision through skin, fat, and muscle. First step: Cavity being unroofed by the subperiosteal resection of ribs.

Figs. 170-174 illustrate the several steps in operation, which I have performed with satisfaction. It is designed to combine the effects of the Schede type of osteoplasty with the added

filling tendencies of muscle implantation. Reference has been made above to the unwillingness of the restored skin and muscle-flap in the Schede operation to slump into the unroofed cavity. It tends rather to bridge it. In Fig. 173 the Schede flap is turned upward, exposing the section of the latissimus dorsi muscle which forms its inner surface. The muscle has been split: one-half has been sutured into the base and upper portion of the cavity; the other half remains *in situ* and will next be separated from the fat layer of the flap, and likewise sutured to the floor of the cavity. If, now, the skin-and-fat-flap should be stitched down in place, it might again bridge as a tight membrane, leaving a new space between it and the implanted muscle. This skin-and-fat-flap then is divided vertically. A triangular piece of the flap is removed from the curved edge (Fig. 169). The U-shaped flap is thus converted into two lateral ones. The newly incised edges can slump toward the depressed muscle, to which they will again become adherent. Through the triangular wound the muscle surface and the unfilled lower portion of the cavity are accessible for cleaning, packing, and stimulation.

Let there be no misrepresentations regarding this method; it likewise has its limitations and discrepancies. The U-shaped flap, even when cut to include a long tongue of the latissimus, yet contains too little muscle to fill cavities of more than moderate size. In fact, the muscle flap may be said never completely to fill; it merely occupies a greater portion of the cavity; there must be sufficient space around it for drainage of the temporarily persisting cavity secretions. From the nature of the discharge a few days after operation, it may be presumed that the buried tip of the flap is ill nourished and partially sloughs. Nevertheless, much has been accomplished in filling, and at least two new muscle surfaces have been provided, which, unlike the pleura, will generously granulate and further hasten the obliteration of the cavity.

Yet one more scheme of operative treatment I mention because of its particular usefulness in certain instances. It was suggested by the observation of a small empyema cavity—the persisting portion of a huge cavity which had been subjected to several obliteration

ing operations of different types. The stitches of the skin-flap had been removed prematurely after operation, permitting retraction of the flap with complete exposure of the small cavity lying beneath. The pleural lining was at first gray and slimy, the secre-



Fig. 176.—A, The infolding of two lateral flaps. Ribs, intercostal tissue, and parietal pleura have been removed. Flaps sutured to lateral wall of cavity. Cavity exposed for packing and stimulation of granulations and epithelial growth. Cavity also accessible for skin-grafting. B, To illustrate inverted T-shaped incision producing lateral flaps.

tion abundant and purulent. It was a most convenient wound to dress; a small gauze packed into the cavity was self-retaining. Eventually the leathery, unhealthy pleural surface acquired a granular, reddish covering; the secretions diminished; the patient improved. Balsam of Peru was added as a stimulant to granula-

tion. The epithelium of the skin bordering the edge of the cavity was rapidly replacing the new granulations; the cavity was being skin lined—not obliterated. A local depression in the chest was present, but complete healing was prompt, the patient having been particularly free from evidences of absorption during his convalescence.

In two subsequent cases larger cavities were intentionally left entirely uncovered. One was at first doubtful as to the safety of such exposure. Again in each instance the gray pleura took on a



Fig. 177.—Muscle implantation. Cavity of moderate size. Wound healed except over small granulating area representing remains of excised triangular segment of flaps. (See Fig. 174.)

thin growth of granulations, which might even have been skin grafted in addition to the epithelialization of the borders.

From these observations an operation was performed on three later cases, such as are described in Figs. 175 and 176. They were high anterior cavities in which the clavicle and first rib restricted shrinkage and obstructed filling. A vertical incision was made, across the lower end of which a shorter curved cut was added. The wound was thus inverted T-shaped (Fig. 176, B). The two lateral flaps were then dissected from the chest-wall. The entire cavity was then unroofed of ribs, as in the Schede operation (Fig. 175). The

lateral flaps were laid over the rib ends in the fashion of the pathologist who would protect his rubber gloves from lacerations during postmortem examination of the thorax. Interrupted silkworm sutures were placed to approximate the skin-edges to the depths of the lateral walls.

It is quite obvious that the innumerable failures in the treatment of chronic empyema are not attributable to a paucity of methods. They are more probably due to an inaccurate conception of the type of cavity to be obliterated in a given case; to the choice



Fig. 178.—Operation by method of infolding lateral flaps. (See Figs. 175 and 176.) Cavity exposed for stimulation and grafting.



Fig. 179.—Large lateral cavity obliterated in seven months by three operations of Schede type. Note elevation of shoulder and lack of extreme deformity.

of some one method ill adapted to the obliteration of a particular cavity; to lack of pertinacious persistency in executing the several stages of the several methods.

The obliteration of a chronic empyema cavity is a problem in mechanics. The equipment of many surgeons consists solely in a knowledge of the technic of some one of the standard operations. Such is inadequate for the proper handling of these cases. A discriminate combination of the more effective features of several or all the types of surgical treatment effects most often a cure. For

example, given a cavity of the type illustrated in Fig. 156: The cavity is first carefully outlined with the aid of the probe, the barium-soaked bandage pack, and stereoscopic radiography. A decortication operation is planned and executed. In the fourth week of convalescence the cavity is again outlined. The lung is found to have retracted again, not to its original position, but to a disappointing degree. Two months are properly allowed to elapse to permit the normal shrinkage of tissues and to restore the patient to suitable resistance. An Estlander or Wilms operation is then made, to flatten the convexity of the ribs and to further shrinkage. Three or four months later the cavity is shown to spread over a smaller thoracic area; it is narrower and deep only in its central portion. A local filling method is chosen—perhaps of the Schede type, or the latter combined with a muscle implantation—or with a skin lining procedure. A due interval is again permitted, after which the degree of obliteration is determined. The barium pack may now outline a tube-shaped cavity of not more than three or four ounce capacity (Fig. 169). Such a cavity might persist for months; it is, therefore, injected with Beck's paste. Sterilization of the space occurs; the skin closes; nature may then be expected to complete the obliteration without incident.

By such a sequence of therapy a large chronic empyema cavity may be cured within twelve or fourteen months. No operation has been of a dangerous magnitude because a surgeon conversant in the methods at his disposal realizes the necessity of the several stage campaign and willingly closes each stage at the moment which is consistent with the prompt recuperation of the patient.

NON-STRANGULATED DIAPHRAGMATIC HERNIA DUE TO INDIRECT INJURY *

DONALD C. BALFOUR

Traumatic diaphragmatic hernia, though not exceedingly rare, is always a surgical curiosity. The condition presents features of interest, as well as problems of considerable perplexity, since the successful repair of the injury may often be associated with baffling technical difficulties. Many of the large number of cases which have been described in the literature were found either at autopsy or when operating in an emergency, immediately after the injury or later, for strangulation.

Reports of the radical cure of chronic non-strangulated diaphragmatic hernia of the traumatic type are, however, surprisingly few, and particularly rare are cases in which the abdominal route has been used. Binnie,¹ in 1914, stated that two cases only of the radical cure of strangulated diaphragmatic hernia were on record. These were both repaired through the thorax. McGuire² has had two typical cases. He used the transthoracic operation and thinks highly of it. I have recently had the opportunity to observe and then to operate by the abdominal route on a hernia of this type, and certain points noted, particularly in reference to the diagnosis and operative treatment, seem of sufficient value to be placed on record and to warrant a description of the case.†

The patient (136,932) was a railroad conductor, forty-seven years of age, who dated all the symptoms of which he complained from a railroad accident four years ago (August, 1911), when he

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† Dr. Crispin diagnosed the case and furnished the records for the history.

was crushed under logs falling from a car. The severity of the injury may be judged from the fact that he was unconscious for six days, with loss of bladder control for twenty days.

The patient's subjective symptoms were briefly as follows: Following the accident and the return of consciousness he began to suffer greatly from gastric distress, which continued unabated and with spells of exacerbation up to the time of our examination. The distress, which was characterized as burning and crowding pain, at times increasing to a colic, began in the epigastrium, and radiated toward the left and into the left chest. It came on, as a rule, about two hours after meals and often lasted from twelve to twenty-four hours. The first solid meal he ate, one month after the injury, "nearly killed him." Since the accident he has not been able to eat heavy food, and he has never obtained relief from any kind of diet, ingestion of food always aggravating the symptoms. There was a marked dyspnea for many days following the injury, and he was not able to lie down in bed. Gradually this became less evident. He was frequently aware of gurgling and rumbling in the left chest. Strong cathartics were continually necessary, and free evacuations were followed by temporary ease of abdominal distress.

Physical examination of the chest disclosed several very interesting facts. The heart was displaced to the right, lying more or less in a median position. The auscultatory signs over the left chest suggested the diagnosis. Under forced respiration splashing sounds of fluid and air were heard as high as the left nipple to the left and above the apex. There appeared to be good expansion in the left upper chest, and the breath-sounds were not greatly impaired. An area of tympany existed back of the posterior axillary line and reached up to the scapula. The physical signs showed considerable variation under different postures; for example, when the patient was put in an exaggerated knee-chest position, the breath-sounds in the left chest became markedly suppressed and the percussion-note lacked the resonance of the right side. When he was in a sitting position, tympany disappeared. Litten's sign on the right side was well marked and definite; on the left side, however, it was absent, and in its stead there was an upward filling of the fourth and fifth intercostal spaces anteriorly from the left sternal margin to the nipple-line.

Fluoroscopic examination showed the left diaphragm at about the fifth space or sixth rib. Gas-bubble in the stomach reached to the fourth rib. The left diaphragm did not reverse with respira-

tion, but action was greatly delayed in the usual direction. The roentgenogram, after using bismuth in both stomach and bowel, showed the stomach to lie high in the left chest; it was distorted

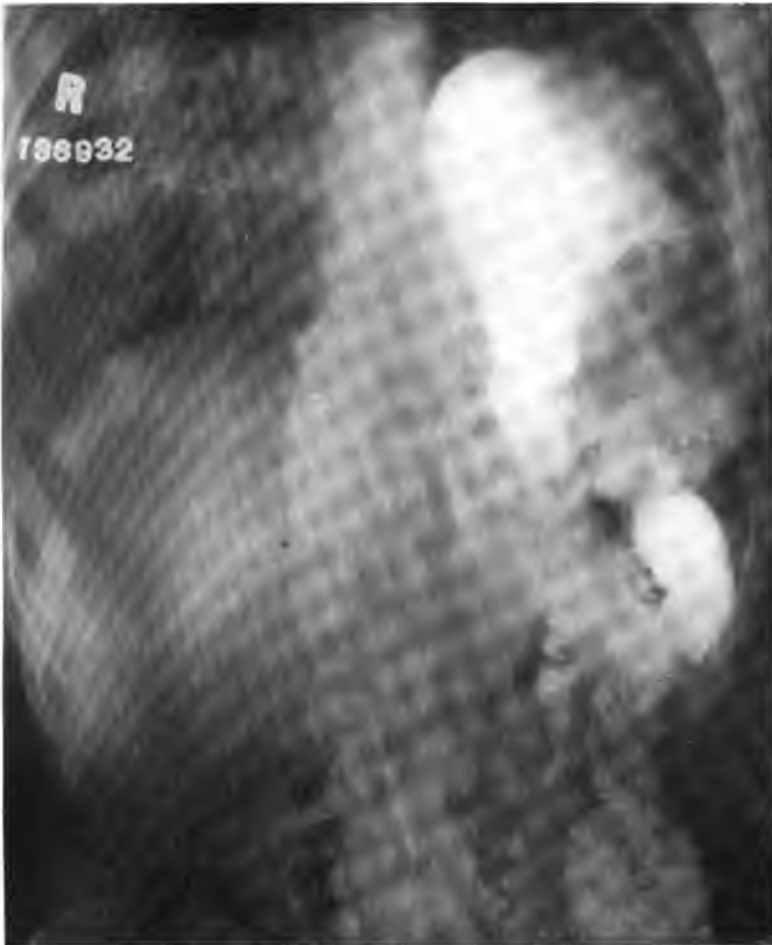


Fig. 180.—Stomach in the left chest.

and partly rotated. The colon occupied the upper part of the left thoracic cavity, the splenic flexure rising above the level of the sternoclavicular union (Figs. 180 and 181).



Fig. 181.—Colon in left chest.

In 1912 Giffin³ made an extensive review of the literature and presented the detailed history of a patient examined and operated on by W. J. Mayo. He called attention to the important points of differential diagnosis. One of the most difficult differentiations is between traumatic diaphragmatic hernia due to indirect injury and elevation of the diaphragm (eventration). This depends largely on the roentgenologic findings. The most important evidences in favor of hernia are: (1) A destruction of the definite dome-shape, which is characteristic of the normal line of the diaphragm; (2) the appearance of lung tissue through the gas-bubble in the left chest; and (3) the demonstration of bismuth in the colon above the level of the bow-line in the chest. The findings in my case corroborate Giffin's statement as to the importance of the position of the colon with reference to the level of the bow-line in the chest. This point has not been emphasized in the literature, but the finding in my case left no doubt that the condition was due to diaphragmatic rupture rather than to elevation of the diaphragm.

Operation (August 7, 1915).—Performed under intratracheal ether anesthesia (Robinson method and apparatus⁴) with the patient in a moderate reversed Trendelenburg position. The Bevan incision was made at the outer border of the left rectus, and continued up to and along the left costal margin toward the midline, an incision similar to that used in performing splenectomy. It was immediately evident that several feet of jejunum had entered the left chest. This was removed, and it was then possible to introduce a hand in front of the colon and stomach and, by careful traction on these viscera, with the aid of the hand in the thoracic cavity, all the displaced abdominal organs except the spleen were evacuated. This was not easily accomplished, since with each inspiration the organs were sucked back into the chest with the most surprising force and rapidity. Adhesions complicated the removal of the spleen, and it was the last organ to be replaced. No serious damage was inflicted, however, the two superficial lacerations being later repaired by catgut sutures. Having succeeded in replacing the various organs in the abdominal cavity, long retaining packs were introduced, and with the aid of the spread-out hands of an assistant the stomach, colon, and spleen were prevented, with considerable difficulty, from being sucked back into the thoracic cavity.

An opportunity to view the defect in the diaphragm was then afforded for the first time. The opening occupied the central part of the left half of the diaphragm; it was roughly circular in outline, with its greatest diameter anteroposterior and the average diameter about seven inches. The edges of the opening were thickened and rounded, and appeared as if they would lend themselves to direct apposition without the necessity of "freshening" the edges.

The method of closing the defect, while simple, is perhaps deserving of particular reference, as it undoubtedly facilitated a satisfactory closure. A long strand of double No. 2 twenty-day chromicized catgut was used. The suturing began at the anterior part of the opening, this being the most accessible part of the defect; the edges of the opening were approximated by the running suture, aided by traction forceps placed at suitable points beyond the margins (Fig. 182, A). The suturing was continued until about two-thirds of the opening was closed, when it was found that the remaining posterior one-third of the defect, which was the most difficult of access, could be best obliterated by picking up the most distant edge of the opening and the closure continued on a line at right angles to the first part of the closure (Fig. 182, B). This permitted not only complete apposition of the margins of the opening with a moderate amount of tension, but also a certain amount of overlapping. Interrupted reinforcing sutures of doubled fine silk were now used to protect the continuous line of absorbable suture material.

More careful examination of the stomach showed the presence of two ulcers, the larger one on the lesser curvature, $1\frac{1}{2}$ inches from the pylorus, forming a suspiciously hard mass the size of a walnut; the second, at the outlet of the stomach, on the posterior wall, and seemingly causing slight obstruction.

The etiologic factors of the gastric lesion are problematic, but it is very suggestive that all this patient's gastric trouble dated from the time of his injury, and it is more than possible that the new position of the stomach in the chest, with the attendant unusual tension, thus rotating the stomach in such a way that the lesser curvature impinged on the margins of the opening, may have been the real factors in the production of the ulcers. It will be very interesting, therefore, to follow the future history of this patient to determine whether the replacement of the stomach to



Fig. 182.—A, Defect in diaphragm exposed. Continuous suture of double chromic catgut begun.
B, Method of picking up the posterior margin of diaphragmatic opening.

its normal position will be followed by relief of the gastric symptoms.

From the surgical standpoint the choice of the route used to gain access to the damaged diaphragm lies between the thoracic, the abdominal, or both. Many surgeons have advocated the transthoracic operation, but in previous cases from our clinic reported by Beckman⁵ the abdominal route seemed to be indicated. It was particularly satisfactory in the above cases. Advantages



Fig. 183.—Roentgenogram of stomach following operation.

may be claimed for each method, and, while in certain of the non-strangulated chronic types of diaphragmatic hernia the thoracic route may be advisable, inasmuch as complications may call for the abdominal route, it is well to be familiar with the method. While Binnie's¹ excellent statistics show a much higher mortality by the abdominal route, it should be remembered that his figures were based on emergency cases, and that in this group of acute cases (stabbing injuries, gunshot wounds, etc.) the very urgency

may be due to the serious damage of abdominal viscera, with the necessity for the abdominal route in these more critical cases.

The patient in this case was ready to go home three weeks after operation, when he developed a subacute intestinal obstruction and an emergency operation was done. A loop of small intestine was found adherent to the original incision. Separation of this was followed by relief of symptoms and good recovery. Thus far there has been no recurrence of gastric distress. Before he left



Fig. 184.—Colon following operation.

the clinic a careful record was made of the physical findings, which showed that the lung was rapidly expanding and the heart assuming its normal position. Roentgen examination of the stomach and colon showed them in their normal positions (Figs. 183 and 184).

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DESMOID TUMORS: REPORT OF TWO CASES IN WHICH THE TUMOR OCCURRED IN THE OPERATIVE SCARS *

DONALD C. BALFOUR

Benign tumors due to the circumscribed overgrowth of normal tissue, such as the lipoma, fibroma, myoma, chondroma, and osteoma, are common. Probably the most frequently seen are those composed of connective tissue, the fibromas.

A well-defined and interesting group of these connective-tissue tumors occur in the abdominal wall. To these Mueller, in 1838, applied the term "desmoid," as designating not only the gross appearance of the oval-shaped enlargement, but also the characteristic arrangement of its fibers into bundles.

That desmoid tumors are not rare is indicated by the paper of Pfiefer in 1904, he at that time having collected more than 400 cases. Many writers, *e. g.*, Morrison, Drummond, Lockwood, Powers, etc., include, in reporting their cases, the malignant neoplasms, of which the sarcomas are the most common, with the benign fibroid type. Whether all isolated new-growths, benign or malignant, in the abdominal wall should be classified as desmoid is open to question. The series in our clinic which I have reviewed have all been of the benign type, and I shall not, therefore, consider the primary malignant tumors of the abdominal wall.

A few facts concerning desmoids may be noted as follows: They occur most frequently in women in the ratio of 7 : 1. The average age of patients is thirty-four. The tumors are always in the anterior or lateral abdominal wall, and although they may occur

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in any part of it, in 43 per cent. of the cases they are associated with the rectus muscle or its sheath, particularly the posterior part. Their relative frequency following repeated pregnancies is un-



Fig. 185.—Gross specimen, desmoid tumor.

questioned. In this connection fibromas of the round ligament have been reported and classified by certain writers as desmoids.

The tumors are usually small, but they may become as large as

the head of an adult. The surface is smooth unless the tumor has reached great size, when it is occasionally lobulated (Fig. 185). All conform more or less to an ovoid shape, the long diameter being parallel to the fibers of the muscle. The cut surface of the typical desmoid presents a wavy, glistening white surface of fibers intimately interwoven and arranged in bundles. Microscopic sections show a solid, fibrous connective-tissue overgrowth (Fig. 186). As in other fibromas, the blood-supply, as a rule, is poor, so that

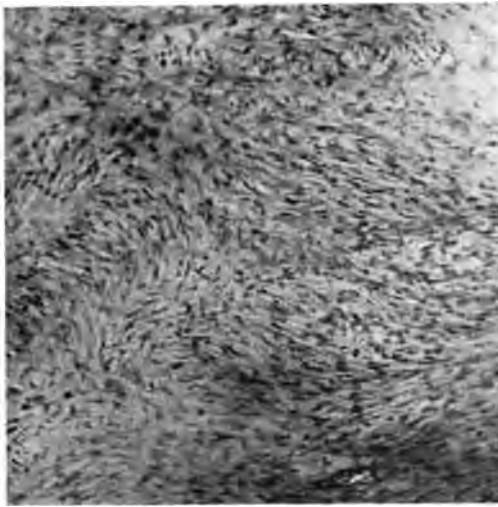


Fig. 186.—Microscopic section, fibrous connective-tissue overgrowth.

necrosis may occur. This condition was observed in one of the series.

The etiology of desmoids is obscure. Traumatism coincident to the repeated stretching of the abdominal wall is the most acceptable explanation for their relatively frequent occurrence in women who have borne children. There must be, however, a predisposition on the part of the person toward overgrowth of connective tissue, which, possibly prompted by a local injury, tends to its proliferation. Such a predisposition is unusual, however, just as is the tendency to keloid formation in operative scars.

Seven cases have been collected from our clinic. In two of this group typical desmoids developed in close relationship to an abdominal incision, and to these I wish to draw particular attention.

CASE 29,486.—Miss E. K., aged forty-four years. In 1900 the patient had a cholecystostomy in our clinic for chronic cholecystitis, and an appendectomy for chronic adherent appendicitis. The incision was made through the upper right rectus. The patient made a satisfactory recovery and was relieved of her symptoms. About a year after the operation a small ridge was noticed in the scar. This increased in size steadily until, within six months previous to her second operation, it had become quite a noticeable tumor. The patient said there was slight tenderness in the mass, especially in certain postures. Exploration and removal of the mass on March 25, 1915, showed it to be a desmoid tumor, involving the muscles immediately below and to the outer side of the incision.

CASE 72,024.—Mr. C. H. T., aged forty-four years. In 1912 a posterior gastro-enterostomy was done on this patient for a large indurated duodenal ulcer. He recovered uneventfully from the operation, and had no subsequent digestive difficulties. In January, 1915, he noticed for the first time an induration immediately to the right of the incision. This did not cause any particular distress, but since it was growing perceptibly larger, an investigation seemed advisable. It was found to be a typical desmoid of the right rectus, lying just outside the incision, but not involving the scar. About two and one-half inches of the upper right rectus were involved and excised with the tumor.

Standing alone, such a sequel suggests that the incision was the main factor in the production of the new-growth. But not only are these the only cases we have observed in this clinic, they are also, as far as I am aware, the only ones reported. The great rarity of such a sequel renders a satisfactory explanation difficult. That such an occurrence is the result of an unusual individual tendency toward connective-tissue proliferation, associated with the local injury, is probable, but not certain.

The rôle of an injury, if it be an etiologic factor, is problematic. A small rupture or split of the muscle or sheath could, in the process of nature's effort to repair the defect, serve as a focus for the

further infiltration of connective-tissue cells, and finally tumor formation.

A positive diagnosis of these cannot always be made. In some instances it is even difficult to determine whether or not they are intra-abdominal, and they have been mistaken for a distended gall-bladder, pyloric tumor, pelvic tumor, and an appendiceal abscess. In one of our cases, in which a large mass existed in the left hypochondrium, the enlargement was thought to be splenic. However, first bearing in mind the possibility of such growths, mistakes in diagnosis will be less frequent. Their somewhat characteristic shape, their fixity in the same direction, and their mobility across the fibers of the muscles or aponeurosis, their palpability when the abdominal wall is made rigid, and the absence of tenderness, are all important points to be noted. When it has been determined that the tumor is in the abdominal wall, malignancy, either primary or metastatic, abscess or hematoma, must, if possible, be ruled out.

Indications are clear for the surgical treatment of these tumors. Wide excision, which may occasionally necessitate the sacrifice of muscle and aponeurosis, to an extent requiring plastic closure, is important. Richardson reported a case in which a transplantation of fascia lata was employed to repair the resulting defect in the abdominal wall. A certain percentage of isolated tumors of the abdominal wall are malignant, and in some instances the malignant character is not evident, even when the mass is exposed. Therefore total excision, avoiding incision of the tumor, is of first importance.

VARICOSE VEINS *

DONALD C. BALFOUR

Varicose veins indicate a chronic dilatation of the veins, the most commonly affected of which are the hemorrhoidal, the spermatic, and the long saphenous. I shall briefly review some of the important features of the condition when it concerns the long saphenous, and present statistical evidence of the results of surgical treatment.

The condition usually occurs in the middle decade of life, although I have observed several patients who were under twenty-five years of age. The ratio of male and female in this series is three to one.

Pelvic tumors, diseases of the heart, and operations on the extremities (osteomyelitis, fractures, etc.) were predisposing causes sufficiently rare in this series to require mention only. Pregnancy was an unquestioned causative factor. Occupation, particularly when it necessitated prolonged erect position associated with hard labor, was by far the most apparent etiologic factor in the greater number of our cases. Moreover, the anatomic and physiologic relationship of veins, muscles, and fascia in the lower extremities is also important, because, mechanically, they offer abundant opportunity for exciting causes to produce pathologic results. If such excitants, particularly occupation, are not modified or some treatment is not instituted, the initial distention of the veins increases, and becomes permanent with the destruction of the action of the valves. This chronically overfilled condition of the veins produces a primary hypertrophy of the elastic tissues to compensate

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for the increased pressure, which is followed by atrophy, dilatation, and secondary fibrous changes in the walls of the veins.

Variable changes of the skin occur in practically all cases of varicose veins; above the ankles particularly it is shiny, and has a characteristic thin, pale, translucent appearance. Later it frequently becomes hard and has a tendency to adhere to the subcutaneous connective tissue, and the chronic hyperemia sets up a pigmentation which, in long-standing cases, becomes dark red-brown in color. The skin is exceedingly prone to become eczematous; the surface varies from moist to the dry, scaly type.

The frequent association of chronic ulcer is well known. In the present series 40 per cent of the patients had ulcers on one or both legs. These ulcers occur on any part of the leg below the knee, the most common situation being on the inner and anterior aspect, just above the internal malleolus. The chronic congestion of the skin and subcutaneous tissue is a strong predisposing factor to the formation of the ulcer; and a slight injury may be sufficient to produce a lesion very resistant to healthy healing. If such ulcers are neglected, as so often observed in the laborer, they increase to a great size, occasionally almost encircling the limb. They are also subject to malignant degeneration, a sequel which is, however, seen with surprising rarity. Pain associated with the varix is a common symptom. This may be marked, even in cases in which the varicosity is not extreme.

Selection of Cases for Operation.—The large percentage of patients presenting themselves for treatment are suitable for operation, but, nevertheless, careful selection is necessary. With few exceptions, when it can be demonstrated that the deeper veins are competent to return all the venous blood, even though it is undoubtedly true they are involved in the same process in a considerable percentage of cases, the removal or ligation of the superficial veins is indicated. The simple and efficient test proposed by C. H. Mayo some years ago is of great value. If the patient can be relieved, or made fairly comfortable by the use of a well-fitting elastic stocking, the removal of the superficial veins will usually be followed by good results. Further indications for operation are

chronic ulceration, neuralgia, and recurring attacks of phlebitis with thrombosis. The most satisfactory results following operation have been in cases in which the trunks of the veins stood out prominently and the stasis was well marked, while failures have occurred when operation had been undertaken in cases in which a general phlebitis had inaugurated a permanent edema, with little evident enlargement of the veins. Among undesirable types for operation are cases following typhoid, and those associated with great dilatation of the internal and external saphenous and of the suprapubic veins.

Preoperative treatment is occasionally advisable, particularly if there is extensive ulceration, or in cases of recent phlebitis where redness and pain, marking local thrombosis, still exist along the course of the vein. If such patients are put to bed for a few days, with elevation of the feet, the post-operative convalescence will be shortened and a good end-result more probable.

Operation.—Many procedures have been devised for the surgical treatment of varicose veins. They vary from simple ligation (Trendelenburg,¹ 1891) to total excision (Madelung,² 1884) or to anastomosis between the saphenous and femoral (Delbet,³ 1906). The procedure advocated by Schede⁴ (1877), namely, division of the veins between ligatures, is still probably the most valuable when the vein cannot readily be removed.

It is generally accepted, and proved by results, that the subcutaneous extirpation of the long saphenous is the most practical and effectual method of dealing with the condition. The procedure introduced by C. H. Mayo,⁵ in 1900, of stripping the vein by means of a metal ring on a carrier about 12 or 14 inches long, has proved a boon in simplifying the operative treatment of varicose veins. Modifications of this instrument, namely, that of Babcock,⁶ have been used with success. The stripper may be tried in all cases. The operation is conducted as follows:

The long saphenous vein is isolated and divided near the saphenous opening, and the proximal end ligated. The distal end is then mobilized as much as possible by means of a long artery forceps of the Murphy type, and the ring of the stripper introduced

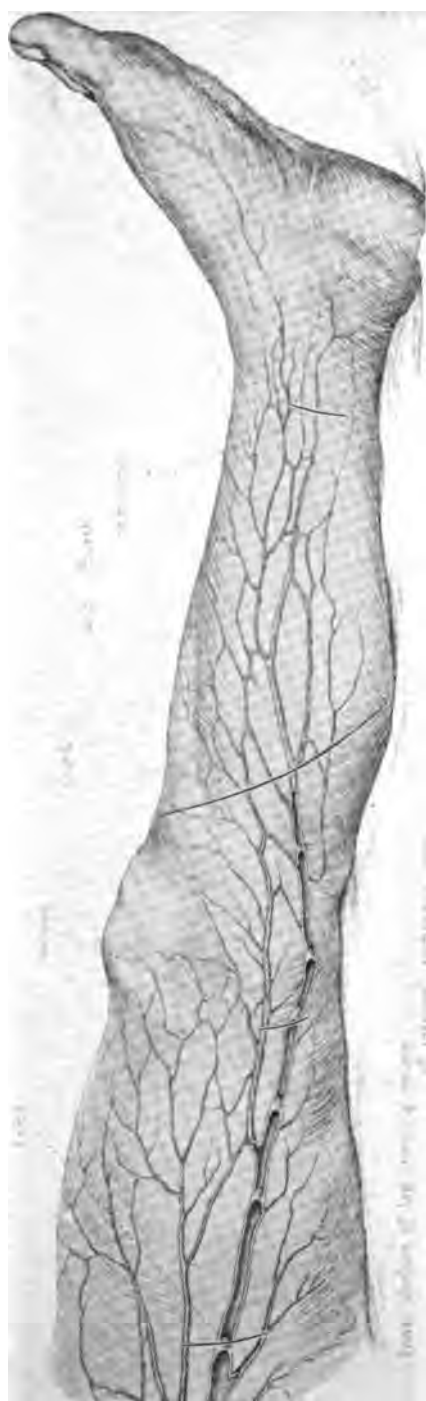


Fig. 187.—Normal internal saphenous vessel, with schematic arrangement of valves.

over the end of the vein. By means of combined gentle traction on the vein with forceps, moderate forcing of the instrument along its course, and with the skin supported by the spread-out hands of an assistant, being particularly careful when the larger branches of the saphenous are encountered, it is possible in most instances to strip the vein down the entire length of the instrument. By forcibly pressing the ring outward against the skin and incising carefully on it, the vein can be picked up and brought out through the small buttonhole incision, and the stripper withdrawn through the first incision. The vein can then be re-threaded on the stripper, and can often be stripped down to one or two inches below the knee, where, however, the main trunk has decreased in size so that the stripping process cannot be continued without breaking the vein (Figs. 187, 188, and 189).

If, as occasionally happens, the saphenous breaks high up, the stripper is discarded, and the trunk picked up through a small incision in the lower third of the thigh, and there ligated. The further procedure in either instance preferred in our clinic is a partial Schede operation for the ligation of the veins of the calf of the leg. A spiral incision, extending from a point close to the anterior border of the tibia, continued backward and downward to a point about the middle of the calf, divides all the main branches of the long saphenous at this level, and gives an opportunity to dissect out any masses of thrombotic or greatly dilated veins, with the overlying skin, if necessary. Having cut these veins between forceps, the second incision is made about three inches above the internal malleolus, and of sufficient length to pick up all the superficial venous branches in that vicinity.

In cases complicated by ulcer and in which the patient has not been kept in bed long enough for the ulcer to heal, local surgical treatment is indicated. Ochsner's⁷ method, a series of short incisions close to and paralleling the margin of the ulcer and encircling it, is most valuable. We have rarely found skin-grafting necessary.

Although the operative treatment of varicose veins has usually been accepted as satisfactory, it seemed worth while to investigate



Fig. 188.—Form and location of incisions for stripping internal saphenous, with mass dissection below the knee.

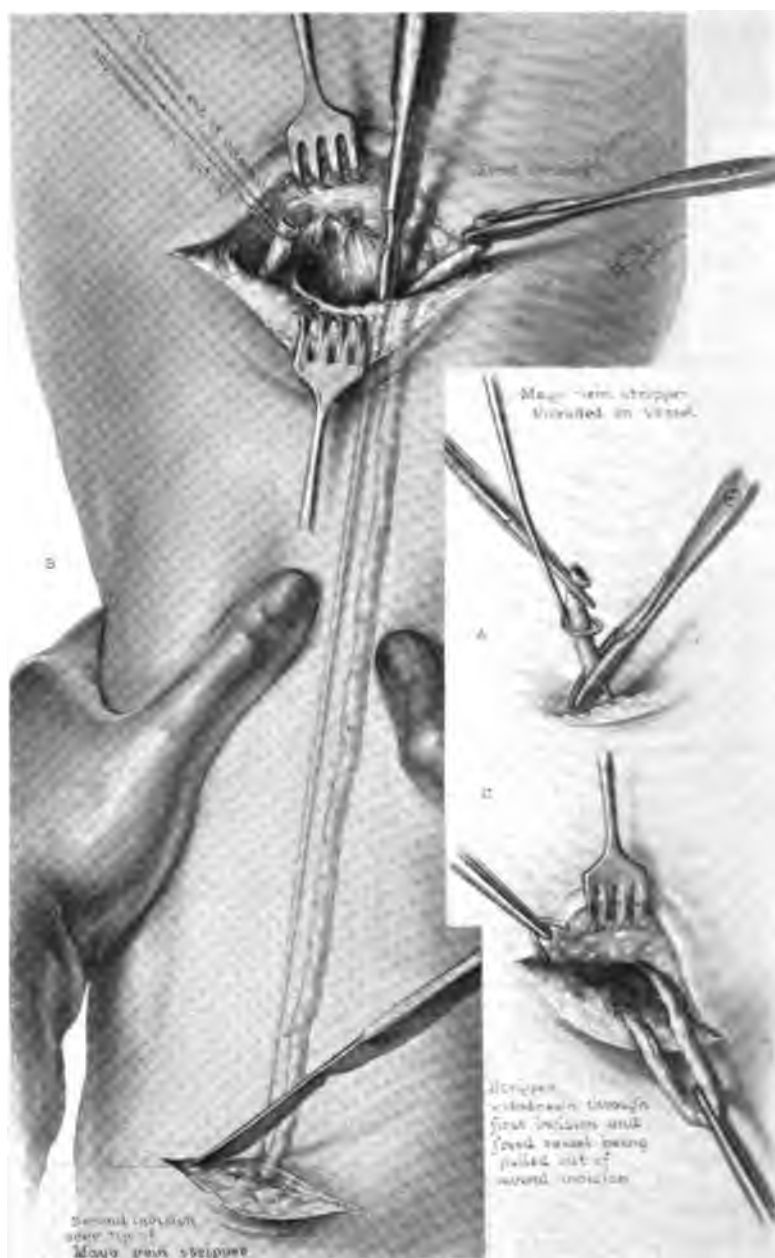


Fig. 189.—Subcutaneous stripping of the vein. Tension on vessel and overlying integument.

the ultimate results, as it is not uncommon to find, on careful investigation in various other surgical procedures, that the results are not quite so successful as had been supposed.

The data for this report on the results of the operative treatment of varicose veins have practically all been obtained by correspondence with the patients. The figures may be considered conservative, for experience has shown that in such investigations the patient is more likely to exaggerate minor unrelieved conditions and to minimize major benefits.

Of 256 patients operated on from January 1, 1909, to January 1, 1914, letters were received from 161; thus in no case has the lapse of time since operation been less than one and one-half years. In 68 patients the condition was associated with varicose ulcer; in 93 there was no ulcer. Thirty-nine (57.4 per cent.) of the 68 patients having ulcer were cured, that is, the ulcer had healed, the veins had disappeared, there was no swelling of the feet, and the patients were able to carry on their work without pain; 16 (23.6 per cent.) reported great improvement, the ulcer having healed in the majority, but minor complaint of occasional swollen feet after a long day's work, or of some aching in the legs; thus 80 per cent. were either cured or improved. In 13 (19 per cent.) the results were definitely unsatisfactory. The ulcer had either failed to heal or there had been periods of complete healing, then pain and swelling sufficient to make the prolonged erect posture uncomfortable. Elastic bandages kept some of these patients in a fair degree of comfort, but the operation itself had failed.

In the 93 patients without ulcer better results were obtained; 67 (72 per cent.) were quite cured, 16 (17 per cent.) were improved, while 10 (11 per cent.) were unsatisfactory, so that in practically 90 per cent. of this group the results were good.

The causes of failures in the series may have been due in part to the selection of cases, incomplete operation, or lack of care in after-treatment. A serious complication occurring with some frequency in the long-standing cases is that the chronic congestion and disability incident to ulcer formation undoubtedly predispose these patients to flat-foot, and the breaking down of the plantar arch is

associated with the familiar pain common to this deformity. The removal of varicose veins in such cases may be successful to the extent of getting rid of the veins, but the expected relief from pain is, of course, not derived.

There were, unfortunately, two deaths in this series from pulmonary embolism, the danger of which in these cases has perhaps been unwisely minimized. This 0.7+ per cent., though small, is not negligible. There was nothing in connection with the operation or the after-care to explain the accident in these two cases. One patient died on the seventh day, before he had been out of bed; the other died two weeks after the operation, when she was about to leave for home against advice.

The operative technic and the post-operative treatment are of importance. The incisions are covered with plain gauze held by strips of adhesive, and the limb, including the ankle, firmly bandaged. Slight elevation in bed is advisable; most patients are out of bed on the eighth day. They are not allowed to be on their feet until they are equipped with elastic bandages, which they have been taught to apply. These are used according to the demands of the individual case, from six weeks to six months.

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IV. THE TRANSPLANTATION OF BONE IN UNUNITED FRACTURES OF THE SHAFT OF THE HUMERUS *

MELVIN S. HENDERSON

A fracture through the shaft of the humerus is occasionally quite troublesome to handle. The patient is able to be about, which makes adequate fixation of the fracture difficult; this is the chief cause of the occasional non-union.

The records of the Boston City Hospital from May 24, 1864, to December 31, 1905, showed a total of 38,627 fractures. There were 3517 fractures of the humerus in this number, *i. e.*, fractures of the humerus formed 10.16 per cent. of the total. The radius was the only bone which was fractured more frequently.

The technic developed in treating 10 cases of ununited fractures of the shaft of the humerus by transplantation of bone seems worthy of presentation. I shall not consider recent fractures. The operation itself is only a part of the treatment; the result which should follow an operation properly performed as to mechanical principles and technic is not obtained if the after-care and retentive splint are omitted. The spica type of plaster-of-Paris case is the most effective fixation for these fractures and can be worn comfortably for months if necessary.

Non-union of any bone is, comparatively speaking, very rare. I mean if the word "non-union" is limited to those fractures in which there is no evidence of union, after the lapse of the normal period of bone repair. In the Mayo Clinic the tibia, more often than any other bone, has been operated on for delayed union.

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If some months can be saved for the patient by so simple a procedure as that of the sliding inlay transplant,¹ when the facts have been presented, he will usually select the operation.

Just when "delayed union" becomes "non-union" is more or less arbitrary, and depends largely on the attitude of the surgeon. Statistics cannot be compiled when the personal equation enters so prominently into the consideration. On examining our records, it would seem as though a pseudo-arthritis occurred more often in the humerus and femur than in any other bones. This condition undoubtedly would be present in many of the tibias but for the fact that the fibula is usually intact or, if fractured, will have united, preventing the free mobility necessary to establish a false joint. In cases where both the fibula and the tibia were ununited there was a typical flail or false joint.

Hamilton² has stated that non-union results more often after fractures of the shaft of the humerus than after fractures of the shaft of any other bone, due to the inadequate fixation provided both at the primary setting and during the convalescent period. Because we have operated on more cases of delayed union in the tibia does not indicate that non-union results oftener in the tibia than other long bones. Many of the tibias that were operated on would undoubtedly have united after more protracted conservative measures. Usually the transplantation of bone was advised and undertaken merely as a means of saving time, which is so important to patients in the active period of life.

The cases used as a basis for this report were all old fractures, and in all the primary setting of the fracture had been done elsewhere. We have as yet to see a case of non-union in the shaft of a long bone which has been treated in our clinic from the time of the fracture. This is the experience of most surgeons, and emphasizes the fact that, with the possible exception of intracapsular fractures of the neck of the femur, cases of non-union are rare. We have greatly curtailed the use of metal plates, wire, etc., and for all delayed and ununited fractures, bone is transplanted whenever feasible.

Two distinct methods are used, one in which the bone is used as

an intramedullary plug (Murphy³), and the other, the inlay method (Albee⁴). Both methods have their merits, but the inlay appeals to one as being the more logical procedure. It is now used in nearly all our work. The chief difficulty in handling these fractures of the humerus is to maintain adequate fixation after the bone transplant has been inserted. To put in the transplant and afterward put on a poor retention-apparatus is a useless procedure in the majority of cases.

Some of these patients present themselves with musculospiral paralysis. It is impossible to know in what percentage of fractures of the humerus this condition is present. Von Bruns⁵ says that in 73 cases of fractures of the humerus there was musculospiral paralysis in 8.4 per cent.

Of our 10 patients, there were three with musculospiral paralysis at the time of examination. The nerve was traced in two of these and the fibers were apparently intact. In another case paralysis of the musculospiral nerve was produced by excessive manipulation and traction at the time of the operation. We knew the nerve had not been severed and a good prognosis was given, but it was four months before there was any return of power and more than a year from the time of operation before complete function was restored.

Technic.—A few days before the operation a spica plaster-of-Paris cast is applied to the shoulder and arm of the fractured side. This gives fixation as nearly perfect as it is possible to obtain; the cast embracing the wrist, elbow, shoulder, and thorax. Before putting on this cast, a dressing is placed on the arm about the size necessary to protect the wound after operation. During the application the wrist is held in mild hyperextension, so that it will be retained in this position, the extensor muscles of the forearm being thus relaxed and not stretched. The elbow is put up in the flexed position, with the arm rotated inward, so that the forearm rests across the front of the body (Fig. 190). If there has been trauma to the musculospiral nerve and consequent paralysis, the muscles will regain their power more quickly on the restoration of a path for nerve impulses, than if the muscles are allowed to remain

stretched. After the plaster has hardened sufficiently to allow cutting with a sharp knife, the cast is split into anterior and posterior halves, which can be readily applied and held in place by adhesive strips after the operation is completed. This method is resorted to, since it is rather difficult to apply a good plaster spica to the shoulder with the patient asleep. Fig. 190 shows a cast which was applied two weeks after operation, and was worn by the patient for four months.



Fig. 190.—Spica plaster-of-Paris case.

An inlay graft, as more nearly approaching the normal anatomic condition, is to be preferred. The sliding method is generally not practical, since in order to obtain a piece large enough very good exposure is necessary and consequent trauma is produced to the muscles and nerves. The graft is obtained from the flat internal surface of one of the tibiae, preferably by the circular motor-propelled saw. It should be long enough to extend well into the sound

bone of the ends of the shaft. A graft 6 inches long by $\frac{1}{2}$ inch wide is the ordinary size desired. A transplant that is too small causes more failures than any other one factor in bone-grafting operations. The failures in our cases may be traced to two causes—too small a graft and inadequate fixation postoperatively and during convalescence. To hold the graft in the trough prepared for it double strands of No. 2 chromic catgut or single strands of kangaroo tendon are used, placing them around the humerus by aid of a ligature carrier. The wound is closed with silkworm and horsehair. The patient is placed in the split spica cast, which is strapped together with adhesive plaster. At the end of two weeks the stitches are removed and a new plaster-of-Paris cast applied. An opening is left over the wound if it is necessary to use further dressings. A brief history of each case is given herewith:

CASE 70,556 (X-ray 16,295).—J. R. B., male, aged twenty-eight, examined by us July 13, 1912, was complaining of non-union following a fracture of the humerus. One year prior to examination a fracture had been sustained of the middle third of the left humerus. The operation was performed July 17, 1912, and a three-inch plug inserted by the intramedullary method. A Lane plate was applied, and a retention splint, merely extending from the elbow to the shoulder, was used. At the end of one year there was no union. On October 23, 1913, a second operation was done, the Lane plate removed, an inlay graft inserted, and a plaster-of-Paris spica applied. A mild infection occurred and persisted until December, 1914, when the transplant was removed at the patient's home. Union was firm at this time, and the discharge from the sinus ceased within five days.

Following the first operation a musculospiral paralysis developed, due to excessive traction at operation. Since it was certain that the nerve had not been severed, a good prognosis was given, but it was four months before there was any return of power and one year before there was complete restoration.

CASE 50,611 (X-ray 11,299).—R. W., male, aged sixty, was examined on March 24, 1911, four months after the fracture had occurred. There was no union at this time. Lane's plate and an ivory intramedullary plug (C. H. Mayo⁶) were used, with resulting non-union and infection. December 28, 1912, the metal plate and screws were removed and a bone plug inserted in the

medulla in spite of a chronic low-grade infection. Later the bone plug was thrown out because of the infection, and the patient lost sight of. At this time union was firmer than at any previous time. This history calls attention to the fact that a patient sixty years of age is not a particularly suitable case for bone transplantation.

CASE 90,547.—H. L. B., male, aged forty-six years, examined August 22, 1913. Eight months previously he had sustained a compound fracture of the humerus and the elbow became ankylosed. August 25, 1913, an intramedullary bone plug was introduced. The transplant broke in two months, the result of poor fixation. No plaster-of-Paris spica was used, and the ankylosed elbow in the extended position made it very difficult to control the arm. This patient has not been traced.

CASE 89,929.—G. A., male, aged fifty-nine years, examined August 13, 1913. He had non-union of the lower third of the right humerus of two months' duration. There had been a compound fracture of the humerus, followed by marked limitation of motion in the right elbow. September 2, 1913, an intramedullary plug was inserted. The plaster-of-Paris spica was not used and the fixation was faulty. A stiff elbow complicated our efforts to control. November 27, 1915, the patient reported that there was no union. The poor fixation and the patient's age were probably responsible for the failure. Roentgenogram showed that the transplant had absorbed.

CASE 92,214.—I. B., female, aged eighteen years, examined September 17, 1913. Fracture of the lower third of the left humerus. Ten weeks after the fracture there was no union demonstrable. October 10, 1913, a bone plug was inserted, as an inlay in the upper fragment, and in the medullary cavity of the lower fragment. A plaster-of-Paris spica cast was used and firm union resulted in three months.

CASE 96,248.—J. M., male, aged forty years, examined November 29, 1913. Ununited fracture of the middle third of the right humerus of thirteen and one-half years' duration. All this time the arm had been used, the patient being a laborer. The roentgenogram (Fig. 191) shows the bone to be of normal density and not thinned out, as are most of the fragments in ununited fractures. A typical flail-joint was present. The man came for consultation because of a musculospiral paralysis, which had been partial for five months, and complete for three months. He was operated on

December 4, 1913, by a combined intramedullary and inlay method. One-half of the transplant was used as a plug and the other half was placed as an inlay in a trough prepared for it. The normal density and properties of the fragments warranted the use of a short graft. The musculospiral nerve was not traced or touched, as it was thought the paralysis was due to the irritation produced by



Fig. 191.—Non-union in humerus of fourteen years' duration. Note the normal density of the fragments.

Fig. 192.—Firm union three months after operation.

the rubbing of the fragments. There was no callus present to cause definite pressure. A plaster-of-Paris spica was applied, and in three months there was firm union (Fig. 192) with full function of the musculospiral nerve. In four months from the time of the operation union was firm and the man was handling heavy timber in a lumberyard (Fig. 192).

CASE 101,653.—M. H., male, aged thirty-eight years, examined March 4, 1914. Ten months before being operated on at the Mayo Clinic this patient sustained a compound comminuted fracture of the lower third of the left humerus, followed by severe infection. At his home, after the wound had healed, metal plates were applied, but non-union persisted. When examined by us March 4, 1914, four months after the plating operation, there was no union and marked restriction of motion of the elbow, possibly 10 degrees being permitted. Musculospiral paralysis was complete. March 12, 1914, we first forcibly flexed the elbow to about a right angle and then transplanted an inlay from the right tibia after removing the metal plates. The musculospiral nerve was not traced, as it was thought that by securing union and reestablishing stability, the nerve would regain its function. The bone-graft used was only three and a half inches long, and this accounts for the slow union (ten months). A longer graft would probably have hastened the union. A plaster-of-Paris spica was applied. At the end of six months the union was apparently solid, but a plaster-of-Paris spica was worn for four months longer, when union was quite firm. Musculospiral paralysis persisted without noticeable gain, and, on September 4, 1915, the nerve was explored and a separation found 3 inches above the elbow. The ends were freshened and sewed together with chromic catgut and silk, the anastomosis being surrounded with fascia obtained from the right thigh. An arthroplasty on the elbow will be done after the return of function to the nerve if no more motion returns in the interim. (Examination November 23, 1915, two months after operation, revealed no signs of return of function in the musculospiral.)

CASE 104,394.—J. H. F., male, aged fifty-three years, examined April 16, 1914, one year after having sustained a fracture of the right ankle and the right humerus; the fracture of the humerus was wired at his home, but six weeks later, while riding on a train which was wrecked, the right arm and right ankle were again injured. Following this musculospiral paralysis slowly came on. Four months later at his home the musculospiral nerve was traced and freed from all adhesions. At the time of our examination a fracture ununited in the middle one-third of the humerus (Fig. 193) was present and musculospiral paralysis was complete. On May 21, 1914, the fragments were exposed and the wire removed. An intramedullary plug was used and many bone chips placed about the site of the fracture. The bone transplant was not more than 3 inches in length. A plaster-of-Paris spica was applied.

The musculospiral nerve was not traced. No union resulted, although the cast was faithfully worn. On March 4, 1915, by the inlay method, we transplanted a piece of bone from the tibia 7 inches long (Fig. 194). August 27, 1915, his physician wrote that firm bony union had taken place. Musculospiral paralysis was still present.

CASE 119,754.—C. B. W., male, aged thirty-six years, clerk, examined November 25, 1914. One and one-half years before



Fig. 193.—Non-union one year after wiring.



Fig. 194.—Long inlay transplant extending well up into healthy bone. Union secured.

he had fractured both tibias, both os calces, and the right humerus. All the bones had united except the humerus, which was fractured in the lower third. This had been wired and plated at his home (3 operations), but no union resulted. December 5, 1914, the ends of bone were exposed and Lane plates removed. An intramedullary transplant was inserted and many small pieces of bone placed about the line of the fracture. A plaster-of-Paris

spica was applied and worn for six months, but no union resulted. Again, May 5, 1915, he was operated on and the inlay method used. Two weeks after the operation the split-cast was removed and a new one applied, which was worn for five months, when union was found to be firm.

CASE 107,886.—L. R. H., male, aged thirty-three years, farmer, examined June 11, 1914. Two years before this man sustained a simple fracture of the left humerus; at twelve weeks there was no union, and in June, 1914, an intramedullary plug was put in by his home physician. No union resulted. On June 12, 1914, we applied a plaster-of-Paris spica, which was worn for six months, but no union was demonstrable on its removal. December 10, 1914, a large inlay graft was inserted and a plaster-of-Paris spica applied. Five months later firm union was demonstrable both clinically and by the roentgenogram.

Discussion.—In the treatment of these 10 cases a technic has been developed which, if carefully carried out, will give a high percentage of successes. That an exact technic is necessary is shown by the high percentage of failures which have occurred by the use of a small graft and a more or less haphazard after-care.

In 9 cases (excluding the one in which there had been non-union for thirteen and a half years) the average duration of non-union before transplantation of bone was twelve and a half months. The average age of the patients was forty-one years: the oldest sixty and the youngest eighteen. But one woman (aged eighteen) was operated on. In 6 the right humerus was fractured, in 4 the left humerus. In 4 the fracture was in the lower one-third, in 6 it was in the middle one-third. Five had been operated on before coming to our clinic. There was an infection present in one at the time of the first operation and in another at the second operation. In four union was obtained by the first operation. In three a second operation was necessary. In two cases we were unable to obtain data as to the ultimate result; in one we know there has been no union; these two cannot be definitely reported upon except to say that, so far as is known, the results in our early cases were not satisfactory. They may or may not have ultimately attained union. Musculospiral paralysis was present in three at the time of our

examination and operation. In one a short time before the nerve had been traced and was said to be intact by the patient's home surgeon. Union of the bone had resulted from our operation, but now, more than one year afterward, there is no return of function in the musculospiral nerve and doubtless it should again be explored. One patient, a brakeman, had the paralysis at the time of the operation and we had intended tracing the nerve, but the implantation of the graft took so long, due to many adhesions and fibrous tissue caused by three previous operations, that no attempt was made to trace the nerve until some time later, when it was found severed. The ends were freshened and placed in a fascial tube made from the fascia lata of the thigh. The result cannot yet be stated. In both of these cases the primary musculospiral paralysis was produced at the time fracture occurred. One case of ununited fracture of thirteen and a half years' duration had a secondary musculospiral paralysis. By the time the bone was completely united the function of the nerve was normal. In one of our early cases, by too free and vigorous retraction at operation a paralysis of the musculospiral was produced which remained complete for four months and partial for one year. There is now full function in the arm.

CONCLUSIONS

1. The transplant must be as large as is practical (6 inches by $\frac{1}{2}$ inch or larger). It must extend well past the thinned decalcified ends into the hard, healthy bone beyond.

2. The inlay is the method of choice.

3. Adequate post-operative fixation is essential. A split plaster-of-Paris spica prepared a few days before the operation can be fastened on with adhesive strips immediately after the operation is completed, thus eliminating the difficulty of applying the spica and the danger of disturbing the graft. Two or three weeks later, when the wound has healed and the stitches have been removed, a new cast can be applied carefully with the patient sitting up.

4. By removing the bone-graft from the flat internal surface of the tibia, the strong crest of the bone is left to perform its important

weight-bearing function. The patient may be allowed to walk in from twelve to fourteen days. At this time the blood clot filling in the bony defect has become sufficiently organized so that no hemorrhages will occur on the use of the leg.

5. A properly applied spica cast may be comfortably worn for three months, when in all probability union will be complete.

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SOME MECHANICAL DERANGEMENTS OF THE KNEE-JOINT *

MELVIN S. HENDERSON

The knee-joint is exposed to tremendous leverage because of its situation between the two longest bones in the skeleton. Mechanically it is constructed so there are practically no bony prominences to strengthen it, thus forcing the ligaments to be the main strength of the joint. It acts as a hinge except at the end of extension, when a screwing inward to a slight degree of the femur on the tibia is permitted. The joint is most stable in full extension when all the ligaments are taut. While the leg is being flexed the joint is a little less stable, and very slight abduction, adduction, or rotation is possible. This slight instability is present to varying degrees up to a right angle; after this it lessens. Considering the apparently poor mechanical arrangement of the articular cartilage and bony surfaces of the joint, it can at once be seen that an extraordinarily efficient ligamentous reinforcement is necessary, and such is indeed provided. A brief description of these ligaments is as follows.

In front is the anterior or big patellar ligament, but as this has a ligamentous or tendinous attachment below and a muscular above, its action as a true ligament is not very great. On the inner side is the internal lateral ligament described as short, strong, and fan-shaped, with the narrow part downward. Its deep portion is intimately associated with the capsule and necessarily then with the internal semilunar cartilage. Its deep fibers are short, thus keeping the internal semilunar close to the condyles of the femur. On the outer side is placed the external lateral ligament, composed of

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two parts, a weak posterior and a strong anterior. This ligament extends from the external tuberosity of the femur to the head of the fibula, splitting the tendon of the biceps in its course. It is sepa-

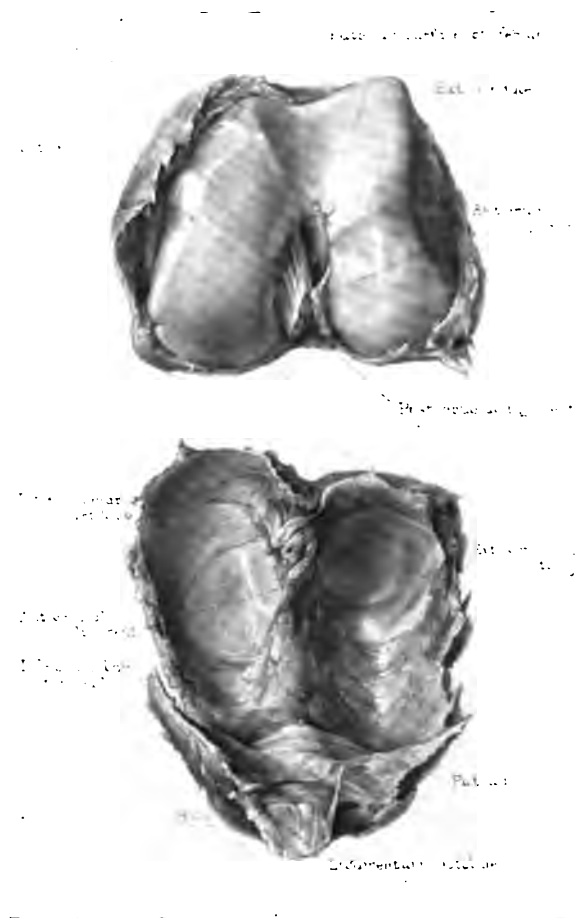


Fig. 195.—Intrinsic structures of the knee-joint.

rated from the capsule of the joint by the popliteus tendon and the bursa found there. These two lateral ligaments are the chief agents providing against lateral mobility. The internal lateral

prevents the knee from bending inward and the external lateral from bending outward. The rounded ends of the femur are buttressed, as it were, by the internal and external semilunar cartilages, thus aiding the lateral ligaments in their function (Fig. 195).

The internal semilunar cartilage forms quite a large segment of a circle and is less movable than the external. Posteriorly it is firmly attached just in front of the posterior crucial ligament. Anteriorly it is less firmly attached just in front of the anterior crucial ligament. Internally it has a firm attachment to the lateral ligament, and somewhat weak attachment to the tibia by the coronary ligament.

The external semilunar forms a smaller segment of a circle. Occasionally it is a complete cartilage, as in the 3 out of the 150 specimens examined by Tenney,¹ there being in these only a small opening against the tibial spine. The external semilunar is fixed anteriorly in front of the tibial spine, posteriorly to the tibial spine between the tubercles, giving a strong slip to the posterior crucial ligament. The attachments to the external lateral ligament and the tibia are very weak. Each cartilage assists the opposite lateral ligament in resisting the lateral movements of the leg, acting as a wedge between the tibia and femur, which helps to make the crucials taut. These semilunar bodies are spoken of structurally as cartilaginous. They are in reality fibrocartilaginous, the thick convex part being largely fibrous tissue, whereas the inner concave portion is cartilaginous. Injuries nearly always occur to this free cartilaginous border, and small pieces of cartilage may become separated and loose. The fibrous tissue is arranged transversely and longitudinally. The longitudinal fibers may continue anteriorly across to the opposite cartilage, forming the transverse ligament—an insignificant structure. At the convex borders the transverse fibers blend with the capsule. The coronary ligaments are formed by these fibers below and are really only the portion of the capsule between the semilunars and the tibia.

The anterior and posterior crucial ligaments are two very important intrinsic ligaments. The anterior arises from the front of the spine near the anterior extremity of the external semilunar and

courses upward, outward, and backward to the inner side of the outer condyle. The posterior arises from the back of the groove at the posterior aspect of the top of the bone, and from its outer border, leaving the floor of the groove and the transverse piece of the spine of the tibia free and covered by synovial membrane. Here it is closely connected with the external semilunar cartilage and runs forward, upward, and a little inward to the front of the outer side of the inner condyle and of the intercondylar notch (Piersol).² These ligaments greatly aid in the stability of the joint. Griffiths³ states that if the internal or external lateral ligament be divided and the lateral bending be attempted in the extended position, considerable bending is allowed, but if the same be attempted in the flexed position no bending is allowed laterally. He concludes, therefore, that bending inward of the knee-joint is prevented by the internal lateral ligament in the extended position and by the crucials in the flexed position. In flexion the relaxation of the internal lateral ligament allows of some rotation. A pull upon the anterior or upper part of the internal lateral ligament makes some traction directly on the internal semilunar cartilage, and this may be responsible for the anterior extremity becoming ripped when caught and extension of the joint is attempted. Jones⁴ says experiments show that hyperextension of the knee is prevented—(1) By the posterior crucial; (2) by the anterior crucial; (3) by the internal lateral ligament, and (4) by the external lateral ligament, and that increased extension is secured as each of these is divided in turn. Internal rotation is limited by the internal lateral ligament and the anterior crucial. In external rotation the tibia may slip slightly forward on the femur, but be stopped by the anterior crucial. On internal rotation the tibia may slip back a little but be stopped by the posterior crucial.

METHOD OF PRODUCTION OF INJURIES

In this series of cases I have taken into consideration only those of internal derangement due to injuries to the semilunar cartilages or to loose bodies having their origin in the joint itself. Foreign bodies introduced from without are not included. The method of

producing these injuries is an interesting subject and is explained in various ways by different authorities. The consensus of opinion is that they usually occur with the knee a little flexed, the foot abducted and everted, thus tending to rotate the tibia outward (or the femur inward). The cartilage is ripped as extension is attempted. Martin⁵ calls attention to the frequency of the occurrence among coal-miners, standing as they do with the knees more or less flexed in low seams (4 feet x 4½ feet in the mines.) A forcible twist or wrench of the tibia on the femur while in this position tends to rip the semilunar cartilage. Walton⁶ believes that injuries to the semilunar cartilages are brought about by a condition of hyperextension of the knee. He says that sudden pain in the joint causes it to be more immediately flexed. The patient falls, and on attempting to rise finds the knee is fixed in the semi-flexed position and believes that the accident occurred with the leg in that position. Jones⁷ says the most frequent cause of injury to the internal meniscus is strain thrown on the internal lateral ligament while the knee is flexed and the tibia rotated outward. In rare instances he has known it to occur with the knee extended. Certainly the histories of cases in our clinic have in the majority of instances brought out the point that the leg was flexed a little, the foot abducted and force applied which caused the tibia to be rotated outward or the femur inward, depending on whether the twisting force was applied above or below the plane of the knee. In some, the records were not clear on this point, the patients themselves not remembering just how the injury was produced. The loose bodies in some instances seem to have originated from direct trauma. The method of production or formation of these loose bodies is not exactly clear, and it may be well to consider briefly their character.

Koenig,⁸ in 1887, described osteochondritis dissecans as being the result of blocking the nutrient end-artery supplying the part in the condyles of the femur. Barth,⁹ in 1896, disputed this, believing that arthritis deformans and trauma were the only two modes of formation of loose bodies of chondral and osteochondral nature. The typical fibrinous bodies are thought to be due to degenerative changes in the synovial membrane, and occur in tuberculosis and

Charcot's joint. Do these fibrinous bodies develop into cartilaginous bodies? Whitelocke¹⁰ thinks they may, and explains the development on embryologic grounds. He states the development of fibrous tissue into cartilage is due to the fact that the early development of the synovial membrane, articular and interarticular cartilages of the knee-joint are all from the same primitive embryonic intermediate layer of the axial blastema. This would indicate that Whitelocke does not favor the view of Koenig as to the origin of these pieces of cartilage. I have seen one case—a young man who had a piece of cartilage firmly embedded in the cartilaginous surface of the femur. According to Whitelocke, this may have originated in a tag of synovial membrane becoming cartilaginous, wandering about and finally embedding itself in the cartilage of the condyle of the femur. To free this piece it was necessary to cut along its edges and lift it from its bed. Clinically, it hardly seemed possible that this piece could have originated elsewhere than from the condyle of the femur. The articular cartilage of the femur is thickest over the trochlear surface on which the patella slides. It is also thickened along the curve of the condyle over the area in contact with the tibia. In this latter area the loosened piece of cartilage was found.

EFFECT OF LOOSE OR FREE BODIES

The primary effect of loose or free bodies is mechanical, chiefly by obstruction of motion and secondarily causing irritation and effusion. Lane¹¹ makes the statement that the large majority of tuberculous infections of the knee-joint originate in the local depreciation of vitality resulting from damage to the internal fibrocartilage. He does not hold that the site of the tuberculous infection is in the fibrocartilage itself, but that the mechanically produced inflammation of the joint causing effusion and inflammation of the synovia may afford the nidus for the infection. Jones says: "An argument in favor of operation is the occurrence of tubercle and so-called rheumatoid trouble as a direct result of the irritation of a displaced cartilage." The irritation produced by these loose or free bodies is chronic and characterized by acute exacerbations. In

some, but certainly not in all, of our cases of tuberculosis of the knee there has been a suggestion of such a history. I might cite an interesting case in this series. A young man had a direct trauma resulting in marked restriction of motion and effusion of the knee-joint. The knee was aspirated, a clear serous fluid being obtained which was used in a guinea-pig test. In a week the joint was opened and a large osteochondromatous mass, which had been demonstrated by the roentgen ray, was removed with a chisel from the region of the tibial spine. An uneventful recovery ensued. The guinea-pig died in six weeks from extensive tuberculous peritonitis involving the liver and spleen. There is no reason to suppose that any error was made in the laboratory, and Sanford says he has never known a guinea-pig to develop a spontaneous tuberculous peritonitis. More than a year has passed since the operation, and the patient has now a perfectly normal functioning knee and is working on a farm.

SYMPTOMS AND INDICATIONS FOR OPERATION

The subjective findings in these cases prove similar, as the histories are reviewed, but the objective findings vary according to the time since the last attack. A typical case of injury to the internal semilunar uncomplicated by arthritis gives a clear-cut history. The injury is most often indirect, perhaps during some not unusual exertion in which the mechanics of the knee-joint are brought into action. The most frequent history is that of an everted foot, abducted leg, and knee slightly flexed throwing stress on the internal lateral ligament. In the act of extension the movement is blocked by the interposition of the cartilage, severe pain is felt, and the cartilage may be fractured. If the fracture is reduced at once and the leg held in extension and quiet for four or five weeks, there will be few cases of recurrence. Too often this is not done and the patient presents himself after many attacks with considerable effusion and perhaps an arthritis.

There has been considerable discussion in the past as to whether the arthritis is a precursor or an end-result of the loose cartilage or free body. A loose internal semilunar scarcely seems sufficient

cause for arthritis, but, on the other hand, a pedunculated or free piece of cartilage might be an exciting cause for an arthritic joint, were the arthritis actually produced by a mechanical agent. We do not know the exact cause of the arthritis. If infectious, the cause may be explained by the theory that the chronic irritation produced in the joint by the loose or free cartilage lowers the normal resistance and devitalizes the entire intra-articular lining, providing a possible nidus for infection. It is quite possible that in many of our older patients the free cartilaginous bodies may have had their origin in the arthritis. Lack of extension or "locking" and the consequent pain are the most constant symptoms, but are not invariably present. Effusion is quite constant, but may be so slight as not to be noted by the patient. Generally speaking, a frank pinching of the internal semilunar produces more effusion than the locking by a free body. This is especially true if an actual fracture of the internal semilunar is produced. A differential diagnosis between a loose internal semilunar and a loose or free piece of cartilage is not always possible. Roentgenograms are our most valuable aid in these cases. The semilunar cartilages do not as a rule cast a shadow. They are composed of fibrous tissue and white cartilage, whereas the free bodies are often osteochondral in character and have sufficient bony deposits in them to cast a definite shadow. On the other hand, a semilunar cartilage which is loose may, through irritation, have sufficient calcium deposited in it or become thickened enough to cast a shadow.

The patients' statements must be carefully considered and weighed. They often say that they have felt the body to the outer side of the joint or above the patella. This, of course, does not exclude a loose internal semilunar, but it does tell us that there is something besides a loose internal meniscus. In the past, the internal semilunar has been given the excess of treatment allotted the appendix in abdominal surgery. The internal semilunar cartilage should be removed only when gross lesions are present or the history is so clear as to leave no doubt. Jones admits that he has sometimes had to close the knee-joint without repairing or removing

anything after having made a careful search for a pathologic reason for the symptoms.

A just balance should be maintained between the clinical and pathologic findings. It is perfectly possible to conceive that between attacks of locking, the cartilage would present relatively little pathology. When a semilunar cartilage is not fractured, or not more than normally movable or thickened, it should not be removed. In America, the literature upon this subject is quite scanty. Certainly the number of knee-joints opened is very much smaller than in England. Whether they are not diagnosed here or whether they are not so common in America is a question. I am inclined to think the latter true. Orthopedists have long recognized that the results of knee surgery are not so good as they should be and have wisely been conservative. Clinical impressions are a poor basis for clinical diagnostic rules.

With the idea of establishing for myself some definite basis for judgment, I began this study. In the Mayo Clinic (January 1, 1910, to January 1, 1915) 63 knee-joints have been opened for damage to the internal semilunar or a loose or free cartilage. In no instance was a damaged external semilunar found. The results in these cases were not all that could be wished. Most of the patients have been seen or have written, giving 52 cases on which to base conclusions. Statistics in such a small group or in any sized group are apt to be erroneous. Operations were performed with practically the same technic. The questions confronting us are—did we cure, relieve, or fail to relieve the patient?

In 60 cases, Finch¹² reported as follows: "In 40, the patients were pleased with the results; in 9 the results were fairly successful, and in 11 not satisfactory." This in the main coincides with our statistics. A careful review of these cases has led me to believe that in the majority of the patients not cured or believing themselves not sufficiently alleviated to justify the pain, inconvenience, and expense of the operation, there was an associated arthritis which might account for the poor result. Associated with the loose cartilage may have been extensive trauma to the ligaments causing an irreparably unstable joint. These patients had expected too

much, an element which cannot be incorporated in our statistics and makes our figures appear even worse than they actually are. However, in summing up, these facts have influenced me very little.

In the entire series of 63 patients there were 7 between the ages of fifteen and twenty; 26 between the ages of twenty and thirty; 12 between the ages of thirty and forty; 11 between the ages of forty and fifty; 5 between the ages of fifty and sixty; and 2 between sixty and seventy. Fifty-two were traced, and of these, 30 may fairly be called cured, whereas 22 did not on the whole have satisfactory results. Expressed in percentages we find 62.5 per cent. cured, 26 per cent. distinctly relieved, but 11.5 per cent. unrelieved. This closely approximates Finch's statistics. Investigating these poor results a little more closely, I find that in 6 cases they cannot be excused on the grounds of associated arthritis, trauma, or poor history. I must conclude, therefore, that the trouble was not located at operation or that the joint was weakened in some way by the operation, *e. g.*, cutting the internal lateral ligament in our attempt to get exposure. The internal semilunar alone was removed in 33 cases, and in 7 together with a loose or free piece of cartilage. In 12 cases a loose piece of cartilage only was removed, the internal cartilage being left unmolested. The poorest results obtained were those in which the internal semilunar and possibly a fat tag were removed in the search for pathology to account for the symptoms. In our experience the fat tag has very seldom seemed to be the offender. When cartilage or fat tags were removed only where definite pathology was found, the results were good. The internal semilunar is needed to strengthen the joint, and if removed is in a measure replaced. In several cases where we have had to explore the joint for some other cause after the removal of the internal semilunar, the space was filled by a firmly fixed fibrous tissue not so large as a normal cartilage, but large enough to be of some help in maintaining the stability of the joint. An associated arthritis in elderly people should not deprive them of the benefit of the operation if there are free bodies or if the internal semilunar is definitely loose or fractured. These people should, however, be told that the operation will relieve the mechanical difficulties, but

not the pain, stiffness, and lack of motion consequent upon arthritis. Unless this is explained they expect complete relief and are naturally disappointed. Arthritis in a young person, consequent to the mechanical irritation of a loose cartilage, tends after removal of the cartilage to improve and may completely disappear.

There was no mortality in this series. Two patients became distinctly worse after operation. One was a woman with associated



Fig. 196.—X-ray No. 21,063. Loose cartilage above the patella, which at operation was found to have moved down between the condyles. Considerable arthritis. Patient, aged sixty, obtained complete relief.

destructive arthritis in which the internal semilunar seemed to be the prime offender. At the time of operation there was no joint fluid present. Removal of the semilunar did not help the condition. The destruction continued and the joint was resected with relief. Bacteriologic tests did not confirm a diagnosis of tuberculosis. In another patient, a young man with an atypical history, a dry arthritis was found at operation. Though there was no fracture, the internal semilunar was removed, since it seemed rather loose and

thickened. A mild infection followed and still persists a year after operation. The joint is slowly stiffening. I believe the arthritis was in process of development at the time of operation in both these cases, and the joints should not have been opened. Such cases should not be operated on.

The operative technic is briefly as follows: There is no preparation of the operative field except thorough washing with soap and water the day before, followed by alcoholic lavage. No water is al-



Fig. 197.—X-ray No. 18,913. Loose body. Free cartilage. Eight years' history of locking followed by effusion. Loose internal semilunar not shown in x-ray.

lowed on the skin on the day of operation. Benzin and iodin preparation is carried out on the table as the patient is going to sleep. A tourniquet is applied. The head of the table is lowered slightly, and the foot-piece dropped, leaving the leg in flexion of about 70 degrees. A curved incision is made along the internal condylar border (Jones) of the femur and the joint is opened, care being taken to avoid the internal lateral ligament. If the internal semilunar is to be removed, it is done usually with a pair of blunt dis-

secting scissors—the posterior end often having to be cut with a small-bladed knife. The capsule is closed with a few interrupted sutures of chromic catgut, and the skin is closed with silkworm gut and horsehair. A posterior splint is applied and the patient allowed to be up on crutches in four or five days. The splint is removed in ten days and moderate active use advised. Weight-bearing is then permitted as soon as the patient wishes.



Fig. 198.—X-ray No 106,288. Shows loose cartilage above patella and faintly one in the intercondylar space.

The following are a few rather typical histories with accompanying roentgenograms:

CASE 83,674.—Woman, aged sixty. Two years before the patient sprained her left ankle and at the same time had a feeling of something snapping in her right knee. She had frequent attacks of sharp pain in her right knee when walking and for a while was unable to move her leg. Roentgenogram showed a loose cartilage in the suprapatellar pouch with hypertrophic arthritis (Fig. 196). Operation May 7, 1913. The internal semilunar, which was dislocated and freely movable, was removed, and also a floating carti-

lage one-third inch in diameter, evidently moved down from its former position between the condyles. Complete recovery followed, showing that age in itself is no contraindication to operation.

CASE 78,990.—Man, aged thirty-two. For eight years the patient complained of painful locking followed by effusion. The last attack occurred two weeks before the operation was performed and was especially severe, suggesting a loose internal semilunar. The roentgenogram showed a floating cartilage, which was re-



Fig. 199.—X-ray No. 106,288 (same as Fig. 198). Shows the cartilage between external condyle and tibia.

moved at operation (January 30, 1913), as was also the internal semilunar (Fig. 197). Complete recovery followed.

CASE 106,288.—Man, aged forty-six. The history in this case extended back thirty-four years, and was characterized by catches of pain in the right knee, not typical but suggestive of locking. At times a loose body could be felt. The patient stated that when bending his knee to sit down he could at times see something snap out at the inner side of the knee. Operation May 28, 1914. Exploration of right knee disclosed the internal semilunar quite loose, one piece of free cartilage the size of a pea in the

suprapatellar pouch and one attached cartilage about the same size between the condyles which were removed. The operation gave complete relief from all pain and inconvenience except that flexion is permitted but a little beyond a right angle. This is improving (Figs. 198 and 199).

CASE 116,019.—Man, aged twenty-four. He had a history of ten years' duration. For seven years soreness in the knee followed walking on rough ground. No swelling, no history of



Fig. 200.—X-ray No. 116,019. Anteroposterior view showing portion of cartilage embedded in internal condyle of the left knee, causing locking, etc.

direct trauma were found. Three years ago he twisted his knee, heard something snap, and had sharp pain over the region of the internal semilunar. Locking occurred and there was an effusion for three or four weeks. A year before and again two weeks before operation the same thing happened. Operation October 1, 1914. The internal semilunar was apparently normal and was not molested. A piece of cartilage the size of a five-cent piece was found embedded in the cartilage of the internal condyle of the femur. It was firmly attached with flakes of fibrin about its edges and had to be cut

free and lifted from its bed. This case seems to be one of osteochondritis dissecans recently described by Ridlon¹³ and others (Figs. 200 and 201). The history suggests that this piece of cartilage becomes dislodged and floats about as a free body, causing locking; later it floats back into its bed and becomes attached for a time.

CASE 97,040.—Man, aged twenty-eight. There was a history of typical locking for twenty years following direct trauma to the inner side of the knee. Effusion never completely subsided. Roentgenogram showed two loose bodies in the joint (Fig. 202).



Fig. 201.—X-ray No. 116,019. Lateral view showing same as Fig. 200.

Operation December 18, 1913. An incision was made in the inner side of the knee. A loose body the size of a quarter and a little thicker was removed. The other body could not be located. The effusion persisted and also the locking. Another roentgenogram two months later showed the second body which was formerly in the posterior part of the joint in the suprapatellar pouch (Fig. 203). April 30, 1914, the joint was again opened through the old incision, as on the operating table the body could not be felt to have moved from its position. A piece of cartilage the size of a quarter and



Fig. 202.—X-ray No. 97,040. Male, aged twenty-eight. For twenty years locking: always some effusion; two loose bodies in joint. The one between the femur and tibia removed at first operation. The other not located.



Fig. 203—X-ray No. 97,040 (same as Fig. 202). Body in suprapatellar bursa was formerly in posterior part of the joint, as shown in Fig. 196.

three-eighths of an inch thick was removed, the semilunar was not touched. The man is now working as a stone-mason with no inconvenience.

CASE 108,373.—Woman, aged sixty. The patient gave “rheumatic” history of twenty years’ duration in finger-joints, etc. Treatment at Hot Springs had given temporary relief. Two and one-half years ago a typical locking of the right knee with associated pain and swelling took place. She had had several attacks



Fig. 204.—X-ray No. 108,373. Female, aged sixty. Hypertrophic arthritis, twenty years' duration. Locking of the joint with typical symptoms for two and a half years. Loose body in the suprapatellar pouch.

with more pain and swelling in this joint. Roentgenogram showed hypertrophic arthritis with a piece of cartilage lying in the suprapatellar pouch (Fig. 204). Operation June 30, 1914. Removal of free cartilage $1\frac{1}{2}$ inches by $\frac{3}{4}$ inch by $\frac{1}{4}$ inch in outer and upper aspect of the right knee relieved the locking and swelling in the joint. There is less pain, but the patient still uses crutches nine months after operation. She is still suffering from the arthritis, but is free from the mechanical difficulties caused by the loose body.

CONCLUSIONS

1. Internal semilunar or external semilunar cartilages should be removed only when definite pathology is present (*e. g.*, fractures, definitely loosened or thickened, and showing evidences of nipping or with so clear a history that there would be no doubt as to its culpability).

2. Loose or free pieces of cartilage should be removed with the least possible trauma. This can be done in some instances under local anesthesia, with, of course, the most rigid asepsis.

3. Small incisions and early use of the leg.

4. The curved incision along the internal condylar line is usually best. In certain selected cases the splitting of the patella, as advised by Jones and more recently by Corner,¹⁴ is an aid in the approach for certain loose bodies, but probably not the best for removal of the internal semilunar or routine knee surgery.

5. Patients, especially elderly people, having associated arthritis cannot expect to be relieved of their arthritis by operation, but are entitled to removal of the mechanical derangements when possible.

6. Under rigid asepsis and careful technic (more rigid than in abdominal surgery), there is practically no danger to life or limb.

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TRANSPLANTATION OF BONE FOR NON-REGENERATION OF THE TIBIAL SHAFT *

MELVIN S. HENDERSON

A girl, aged six years, was brought to the Mayo Clinic for consultation and treatment November 20, 1912. Seventeen months before she had had a typical attack of acute osteomyelitis of the left tibia. On the seventh day an abscess was opened and during the next fortnight several more collections of pus were incised and evacuated. Two months after the onset a subperiosteal resection of the entire shaft of the left tibia was performed by the attending surgeon. At the time of our examination there was non-regeneration to the extent shown in Fig. 205. The child was wearing a brace which enabled her to walk without crutches. The fibula was quite enlarged as a result of the increased function demanded of it. Since the sinuses had been healed only two months, we advised deferring operative interference for three months to make sure that the infection had become quiescent, and to see if by any chance more regeneration would occur, thus eliminating surgery. At the end of this time the leg still looked clean, but no further regeneration had occurred.

February 14, 1913, a piece of bone $4\frac{1}{2}$ inches long and three-eighths inch wide was removed from the opposite tibia and placed in a warm salt cloth while the bed was prepared for it in the affected leg. The periosteum was retained on the transplant, which was wedged into the upper fragment, and side-to-side apposition to the lower fragment was secured. Holes were bored in the transplant and silver wire used to hold it in place, a suture now rarely used in our bone surgery. Fig. 206 shows the graft three months

* Reprinted from Jour. Amer. Med. Assoc., 1916, lxvi, 177-178.

later firmly united above and below with only slight increase in the size of the transplant. During this convalescent period the child wore a cast and was provided with crutches.

Two weeks after the roentgenogram (Fig. 206) was taken the child stepped rather heavily on the left foot while playing and felt and heard something snap. No particular pain was complained of, but a month later (June, 1913) her parents brought her to the



Fig. 205.—Incomplete regeneration of the shaft of the tibia following subperiosteal removal twenty-one months before.



Fig. 206.—The graft three months after operation, firmly united above and below.

clinic for examination. Fig. 207 shows a fracture where the silver wire was thrown around the graft and the lower fragment. The non-absorbable silver wire had caused an osteoporosis here which finally resulted in fracture at the instigation of an unusual strain. Casts and crutches were used for a year in the hope that the fractured graft would unite. In July, 1914, fibrous union only had occurred, but there was marked increase in the size and density of

the transplant. Fig. 208 shows the somewhat wild attempt of nature to bring about union.

It was decided again to remove a piece of bone from the sound tibia as a graft to bridge the fracture in the original transplant, and July 23, 1914, a piece of bone $2\frac{1}{2}$ inches long by three-eighths inch wide was transplanted. The silver wire that was easily accessible was removed. A cast was worn until March, 1915, though weight-



Fig. 207.—A month later than Fig. 206, four weeks after the fracture of the transplant.



Fig. 208.—One year after the fracture of the transplant. Note the callous formation.



Fig. 209.—Restoration eight months after the second operation. Note the beginning formation of the intramedullary canal.

bearing was permitted in three months. Fig. 209 shows the condition April 26, 1915. Note the beginning formation of a medullary cavity in the transplanted area. The child now has complete restoration of function.

The case is thought worthy of report for the following reasons:

1. It emphasizes the fact that non-regeneration frequently occurs after a subperiosteal resection, as advised by Nichols.¹

2. The operation as recommended by Phemister² was probably not done on this child at the right time (two months after onset). A little later enough osteoblasts and new bone might have been attached to the periosteum to insure the regeneration of the entire shaft.

Empirically, no definite time can be set for removal of the shaft. The Nichols operation probably is not used as often as it should be because of this indefiniteness as to the time the shaft should be removed. It would be better to remove the entire shaft, especially in children, and quickly eradicate the disease, if we could be at all sure that regeneration from the periosteum would follow. While in this case the patient has been submitted to three operations, she now has a practically normal tibia and not the hard eburnated tibia so prone to reinfection that occurs in the old chronic cases of osteomyelitis.

It may be better to accept the chance of non-regeneration in these cases of acute osteomyelitis of the tibia involving the large part of the shaft, since bone transplantation or the use of the fibula, as advised by Huntington,³ offers such ready means of controlling the deformity and disability. But these methods cannot so readily be advised, for example, in the humerus and the femur, for here there is no second bone, as the fibula, to assist in maintaining alinement and growth. However, this is not an insurmountable difficulty.

3. Fig. 209 shows how the transplanted bone has taken on the function of normal bone and Fig. 208 shows its attempt, and failure, at union.

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OPERATIVE TREATMENT OF BUNIONS BY THE MAYO METHOD *

MELVIN S. HENDERSON

DEFINITION

The bunion is a painful bursitis superimposed on a hallux valgus. The degree of hallux valgus is by no means a criterion of the severity of the bunion (Fig. 210). The Mayo operation for bunion is for the relief of the painful bursitis, and not a cosmetic operation for doing away with the deformity of the hallux valgus, though incidentally the deformity is reduced. For many years the operation¹ about to be described has been used in the Mayo Clinic and has given such satisfactory results that I think it wise to emphasize its usefulness.

ANATOMY

Briefly, we may consider the anatomic findings in this deformity. It is not seen in children who have never worn stiff shoes nor is it noted in individuals who have always gone barefoot. In these normal feet the great toe is in line with or turns slightly inward from the inner border of the foot. It has been stated that in the bunion foot the great toe is the longest, whereas the second toe should be of the same length or even a little longer. While this is not invariably true, still in this type of foot, that is, with the great toe the longest, the deformity is often present. In hallux valgus a line drawn through the anteroposterior axis of the great toe courses anteriorly outward at an angle of 30 degrees or

* Read before the Section on Orthopedic Surgery at the Sixty-sixth Annual Session of the American Medical Association, San Francisco, June, 1915. Reprinted from *Jour. Amer. Med. Assoc.*, 1915, lxx, 1356-1358.

more. The condition has generally been caused by wearing too short a shoe, and this information is many times voluntarily given by the patient. The tendon of the extensor proprius hallucis becomes displaced outward and further increases the deformity. The pressure and irritation of the shoe cause more or less of a chafing action on the skin over the prominent inner aspect of the



Fig. 210.—Moderate hallux valgus with painful bunion.

head of the first metatarsal bone. This irritation in many cases causes a distinct hypertrophy of the end of the bone and small bony exostoses occasionally form. Nature comes to the rescue with the formation of a bursa and we then have a bunion. It is only when this bursa becomes inflamed, mechanically or by infections, that tenderness results and surgery is indicated. Many cases go on to sepsis. When this occurs, operation should not be

undertaken until the infection has completely subsided. Complete rest and alcohol dressings usually promptly clear up the infection. On top of the bursa may come a corn, adding further to the distress and inconvenience of the patient. Thus it may be stated that the symptoms depend not on the deformity, but on the inflammatory changes in the bursal sac causing oftentimes continual discomfort and pain. The proximal phalanx of the first toe ar-

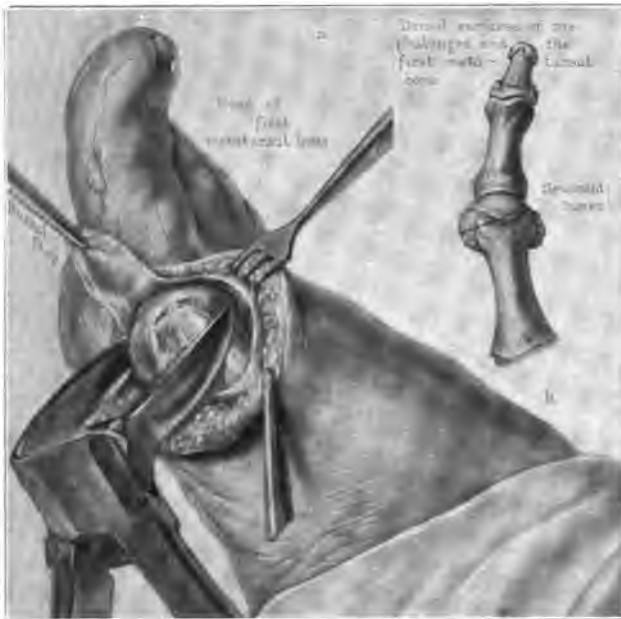


Fig. 211.—*a*, Removal of head of first metatarsal bone. Bursal flap dissected free; *b*, angle at which head of metatarsal is removed, showing short incision at right angles to long incision. The short incision removes the hypertrophy of the bone.

ticulates often only against part of the head of the first metatarsal, the inner portion of the head impinging against the skin of the inner side of the foot. Often in patients in middle life or beyond, rarely in the young, there is an associated arthritis with deposits. These patients do not obtain the great relief accorded the non-arthritic cases. They should not on this account be denied the benefits of the operation, since formation of the new joint is a great relief.

All cases of hallux valgus do not cause inconvenience and many cases of moderate bunion had better not be interfered with surgically. Too often the cases are passed over lightly by the surgeon when the complaint is really a serious and disabling one to the patient and demands surgical interference. Bunion has long been looked on as a trifling condition, but to the individual with the pain it is anything but trifling.

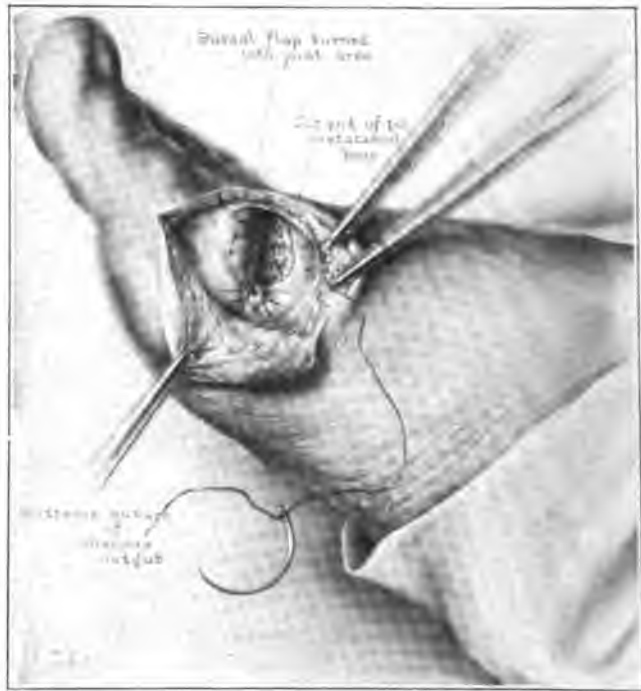


Fig. 212.—Head of bone removed. Bursal flap tucked in and approximated to periosteum of first metatarsal by two mattress sutures of chromic catgut.

OPERATIONS

Heuter² advised excision of the head of the first metatarsal bone for the relief of the condition. Hamilton³ later reported eleven cases, and his name is often mentioned in connection with the operation. Schede⁴ advised excision of the bursa and removal of part of the head of the first metatarsal not in contact with the

phalanx. Barker and Reverdin advised removal of the exostoses and of a wedge of the metatarsal just above the head. Various other operations have been suggested, such as removal of part of the proximal phalanx and part of the head of the metatarsal. It has been suggested that the head of the metatarsal bone be re-



Fig. 213.—Greater part of metatarsal head removed, leaving sufficient of the expansion for weight bearing.

moved by an incision between the great and second toes, thus doing away with an incision on the inner side of the foot. The objection to an incision on the inner part of the foot we have found to be theoretic rather than real. By making a curved elliptic incision with the curve upward, it can be so arranged that the pressure of the shoe comes below and not on the line of incision.

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tarsal phalangeal joint of the great toe. The skin is dissected back, being careful not to puncture it. A flap including the bursa is then taken with its base attached to the proximal phalanx, having its convexity extending on to the head of the first metatarsal (Fig. 211, *a*). The fat is then pushed back from around the head of the bone and a large bone-biter is introduced from without inward, aiming to take off most of the articulating surface of the head of the metatarsal bone, leaving sufficient of the enlarged end to serve as a weight-bearing portion (Fig. 212). This bone-biter is introduced at an angle of about 75 degrees, so that the outer side of the metatarsal bone is a little longer than the inner side after the piece is removed (Fig. 213). With a rongeur bone-biter the prominence left on the inner side is smoothed down (Fig. 211, *b*). The flap is then tucked in and the base of the flap sewed to the periosteum of the first metatarsal by two mattress sutures of chromic catgut (Fig. 212). This serves to straighten the toe and put it in its proper line. The skin is then closed with one or two sutures of silkworm gut and closer approximation is secured by interrupted horsehair sutures. A pad of gauze is inserted between the great and second toes to straighten the great toe (Fig. 214). A dressing soaked with alcohol is applied and carefully bandaged.

AFTER-CARE

No splints are necessary. Pressure of the bedclothes is removed by the use of half barrel-hoops. Twice daily the bandage is opened enough at the end of the great toe to allow pouring in of alcohol, thus soaking the dressing and adding greatly to the comfort of the patient. Stitches are removed in a week, weight-bearing permitted in ten days, and the patient encouraged to use the feet as soon as possible. A small pad of gauze or cotton is to be worn between the first and second toes for a few weeks. The wearing of shoes with a proper straight inner side is insisted on. All patients will not follow this advice, but by carefully explaining why it is to be desired, the responsibility is then placed on them.

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TECHNIC

INTRATRACHEAL ETHER ANESTHESIA: A NEW APPARATUS AND INTRATRACHEAL TUBE *

SAMUEL ROBINSON

After a thorough trial the intratracheal method of administering ether anesthesia has justified its existence. There is but one contraindication to its use; namely, the presence of a profuse purulent bronchial secretion. The method is particularly indicated in:

1. Resections of the upper or lower jaw.
2. Resections of the tongue and floor of the mouth.
3. Operations on the brain.
4. Plastic operations on the face.
5. Laryngectomies.
6. Difficult tonsillectomies requiring careful dissection.
7. Operations for cleft-palate.
8. Removing tumors of the wall of the chest which involve the pleura.
9. Exploratory thoracotomies in the absence of pleural adhesions.
10. Transpleural operations on the heart and esophagus.
11. Extensive plastic procedures for chronic empyema when there is restricted respiratory function.
12. Operations on the lung in certain rare instances.

The definite reasons for the applicability of the method in the above-mentioned instances are as follows:

1. In certain operations on the head it is convenient and desirable to dispense with ether masks, cones, and inhalers which

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tend to soil the sterile field of operation, and since they must necessarily be removed intermittently, uneven and generally insufficient anesthesia results.

2. To remove the anesthetist from the immediate field permits greater accessibility, thus facilitating the work of surgeon and assistants, and diminishing the possibility of errors in the technic of asepsis.

3. The somnolent, peaceful breathing coincident with intratracheal etherization is accompanied by the minimum amount of congestion of the blood-vessels of the head; hemostasis is thus favored.

4. The inhalation of blood, mucus, infectious material, and bits of tissue, not uncommon in routine operations about the mouth and a possible source of complications, is prevented to a considerable extent by the outflowing escape of air around the intratracheal tube.

5. In certain thoracic operations already mentioned in which a free pleural cavity is to be widely opened, it is advisable, and on occasions imperative, to assist the respiratory function by insufflation of the lungs. If the intratracheal tube is already being employed for anesthesia, the additional features of insufflation may be added promptly by certain adjustments in the apparatus.

6. The lungs of certain patients with chronic empyema are restricted in aërating surface. The necessary cramped posture on the operating table further limits the expansion of the better lung. During extensive plastic operations on such patients cyanosis is of common occurrence. The insufflation incident to intratracheal anesthesia accelerates the tidal air exchange, thus relieving cyanosis.

The tube may be introduced into the trachea by any one of several methods:

1. A laryngeal speculum, preferably of the Jackson type, may be used to lift the epiglottis and to illuminate the vocal cords, between which the tube may be directly introduced; an excellent method, requiring limited paraphernalia, slight change of posture, and moderate experience in the use of the speculum.

2. A hollow steel introducer (Cotton) of a caliber sufficient to contain the tube may be used to guide the tube across the mouth and pharynx and to point its tip in the direction of the vocal cords.

3. A woven catheter may be passed directly into the larynx by sense of touch. This procedure, owing to the absence of any guide, is difficult of execution. Trauma may result both from the introduction and from the presence of a stiff-walled tube within the trachea.

After sufficient experience with the above methods I came to these conclusions: (1) That direct vision is not essential for prompt intubation, and that the speculum is, therefore, superfluous; (2) that the hollow steel introducer is an insufficient guide

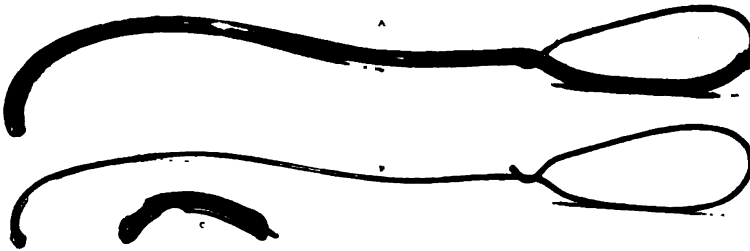


Fig. 215.—An intratracheal tube. A, modification of a type of urethral catheter. B, Olive-tipped, tempered steel stilet to guide intubation. C, End of tracheal tube. Hollow cup at tip for olive stilet; two side eyes.

to the tip of the tube; (3) that a tempered steel stilet within the lumen of the tube and reaching to its very tip serves as a more effective guide; (4) that an inlying soft-rubber tube might cause less irritation to the tracheal membrane than a woven catheter.

Slight alterations in a certain type of stiletted soft-rubber urologic catheter were sufficient to provide the tube and stilet (Eynard) (Fig. 215). The lumen of the tube is of greater proportionate diameter to the outside diameter of the tube than is found in the usual soft-rubber urethral catheter. There are two side eyes, provided as a safeguard against obstruction to the inflowing air and ether. The tip of the tube (Fig. 215, C) is made hollow, and provides a hollow cup to retain the olive tip of the steel stilet, while the

urethral catheter is generally solid at the tip, the lumen terminating in the side eye. These tracheal tubes are now manufactured in sizes from Nos. 21 to 24 F.

Technic of Intubation.—The stilet is bent to a curve adapted to the patient to be intubated. It is then smeared with a thin coat of vaselin and inserted into the tube, care being exercised that the olive tip of the stilet is implanted accurately in the cupped end of the tube (Fig. 215, C). The tube is stretched gently along the shaft of the stilet and held thus by the spring grip of the stilet handle (Fig. 215, A). The outside of the tube is then lubricated.

The patient lying in the flat dorsal posture is anesthetized to the point of complete muscular relaxation. The head is raised with a two-inch pillow and so placed that the face points directly upward. The intubator stands at the patient's right—the assistant opposite. The jaws are well separated with a side mouth-gag. The tongue, seized with rubber-tipped tongue forceps, is drawn forward. The assistant holds the gag in his right hand—the forceps in the left. The intubator then inserts his left forefinger into the pharynx and lifts the epiglottis forward. With the right hand he gently introduces the stiletted tracheal tube across the mouth and pharynx, with care that the plane of the tube is accurately in the median line. He then causes the tip to pass behind the forefinger now supporting the epiglottis. If properly directed, the tube meets obstruction at this point. The vocal cords will approximate themselves in response to the irritating contact with the tube end. Gentle manipulation is indicated here: trauma only increases the spasm of the cords. Suddenly the tube should slip between them, at which moment the patient, unless very deeply anesthetized, will cough spasmodically. This alone is ample evidence that the tube has entered the larynx. With the handle grip released the stilet is cautiously withdrawn with the right hand, the left synchronously sliding the tracheal tube over the stilet into the trachea. Under deep anesthesia or previous laryngeal cocaineization the entrance of the tube may cause no reflex spasms. Doubt may thus arise as to whether the tube is in the trachea or the esophagus. The intubator then places the oral end of the tube

against his cheek. If the tube is in proper position, he will note intermittent breaths escaping from it synchronous with expiration. Meltzer refers to this as an unreliable test, explaining that an esophageal breathing also occurs and may produce the same



Fig. 216.—An ether-vaporizing apparatus for intratracheal anesthesia.

phenomenon. Therefore he suggests that the tube be conducted well down into the throat. If it meets obstruction at a deep level it may be concluded that the trachea has been entered and that the obstructing element is the bifurcation, at which moment it is

withdrawn two inches to its proper final position. If, on the contrary, no obstruction is met in this experiment, it is presumed that the tube has entered the esophagus. Experience nevertheless

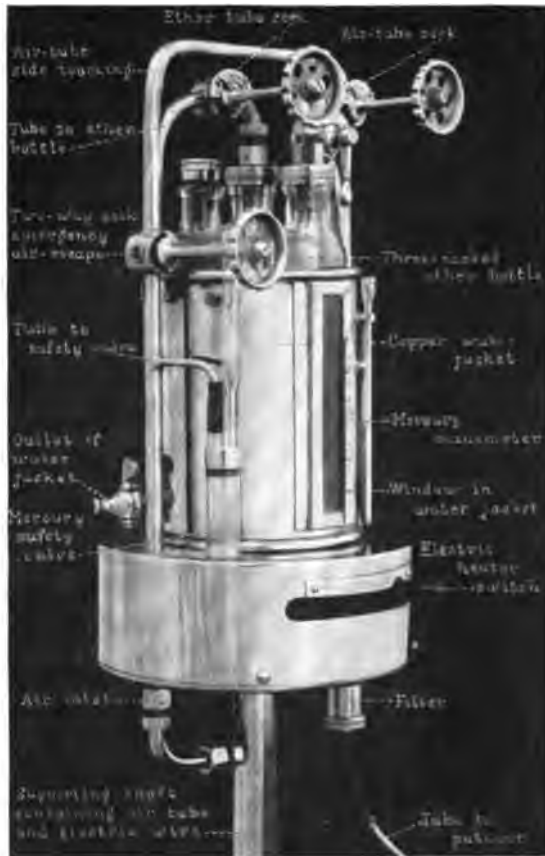


Fig. 217.—Ether-vaporizing apparatus, showing details of upper portion.

soon teaches one to gather definite and prompt conclusions as to the success of his intubation from the aggregate indications.

If the intubation has prompted spasm and coughing, it is sometimes preferable to reapply the ether mask or cone for a minute before connecting the vaporizing apparatus with the tube.

Vaporizing Apparatus.—There are many forms of vaporizing apparatus to provide anesthesia when connected with an intratracheal tube. They vary in size, design, mechanism, and cost, but from the point of view of adequacy of function, they may be said to be equally efficient. Certain features in the vaporizing machines, once regarded as essential, have proved to be superfluous:

1. It was supposed that the entering air and ether mixture must be moistened by passing through water, thus supposedly imitating a function ordinarily performed by the pharynx. Apparatus devoid of such water-baths have now long been used without harm and with equal efficiency.

2. The earlier machines were fitted with connections to warm the entering mixture of ether vapor. It has since been shown that it is not only quite impossible to accomplish this, but also that a mixture arising from a volume of liquid ether the temperature of which has been lowered sufficiently to cause frosting on the outside of its glass container, is yet harmless to the air-passages.

3. Heat devices are yet employed in apparatus to prevent too great a lowering of the ether temperature. The object of this, however, is solely to facilitate the vaporizing of the ether and thus to economize in the amount of the liquid consumed.

4. Bacterial filters were advocated, but there is no evidence that the use of machines not thus provided has resulted in any untimely effects.

Therefore, simplicity of design and increasing lack of cumbersome in apparatus has resulted from six years of clinical application of this interesting method of anesthetizing.

The apparatus illustrated in the accompanying photographs (Figs. 216 and 217) is remodeled from one previously described by the writer.* There are no particularly original features in its construction, and yet it is presented because it has proved itself in a series of 500 cases to be safe, useful, and reliable.

* Apparatus for thoracic surgery under intratracheal insufflation or positive pressure, etc.

STAINING SECTIONS OF LIVING TISSUE, UNFIXED *

LOUIS B. WILSON

The fixation of tissues by rapid killing and hardening before further preparing them for the microscope is now universally conceded as a necessary process in the study of many cell structures. It produces variations in the degree of refraction and degree of imbibition of cells and of portions of cells, thus making possible their optical differentiation. It also prevents postmortem changes in cells, preserving their structures so that they may be studied at leisure. By coagulating fluids and by rendering insoluble certain tissue elements, fixation prevents their removal during subsequent manipulations. By the intelligent choice of proper fixatives and other reagents we may kill, harden, and prepare for the microscope almost any tissue without greatly altering the relative size or shape of its cell elements. The changes in refractive indices and in color reactions, while artificial, are not necessarily misleading, though our concepts of the normal relations of cells are no doubt often greatly exaggerated.

While conceding the necessity for fixation in almost all instances for fine cell study, histologists are well aware of the desirability of studying living cells with the least possible manipulation. But living cells are indistinctly marked off from each other, and their complex internal structures have almost exactly similar refractive indices and little or no color variations. Thus, the microscopic examination of untreated living tissues, in other than ultraviolet light, quickly runs counter to certain fixed principles of physical

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optics. Our problem then is the production of variations of color and refraction with the least violence to the cell and without coagulating its protoplasm.

That cells may be stained in the living animal has been abundantly shown by Ehrlich,¹ S. Mayer,² Apáthy,³ Bethe,⁴ and others. More recently the physiochemical processes by which living cells are stained have been studied by many observers, among them Kiyono,⁵ Michaelis,⁶ and Evans and Schulemann.⁷ The latter observers have shown that the chemical constitution of benzidin dyes is of no influence on the capacity of the dyes to act as vital stains except as it affects the physical state of the solutions of the dyes. Such dyes are taken into certain living cells by the same forces concerned in the reception of large particles (bacteria, carbon, etc.) into cells, forces based upon alterations in surface tension. The diffusibility of the stain determines only its capacity to reach the cells in a living organism. Its inclusion by these cells is not dependent upon a characteristic of the stain itself, but upon the vital functions of the cells.

Thus, by what has long been known as "phagocytic action" living cells take up certain dyes, but the process is a slow one and the ultra-microscopic particles of "colloid" solutions of the dyes are apt to be so grouped in the cells as to form definite microscopic masses, which may be mistaken for cell structures. This method of true vital staining has great possibilities, and its application is yet in its infancy. Its greatest interest, however, apparently lies in its biologic aspects, that is, as an indicator of the differentiation of the functions of the various cells in the living body. The morphologist, and especially the pathologist making microscopic examinations of operative material and working in as speedy a manner as possible, will find more use for methods based on the principle of staining living cells whose surface tensions are already altered, permitting rapid imbibition of dyes.

Many living cells which will not take up certain stains may be made to imbibe them by even so slight an alteration of surface tension as may be produced by shaking the cover-glass on the preparation. Tissue freshly removed from the living body is still

alive and remains so even after it has been quickly frozen, but the surface tension of the cells of the tissue has apparently been materially altered by the cutting off of the blood-supply and by the freezing process. This alteration of the surface tension of the cells permits the rapid imbibition of certain stains, while at the same time the size and shape of the cells may have been altered in only a very slight degree, if at all, by the anemia and freezing. Theoretically it should be possible thus to find just such a stage in cells, which are dying but yet not dead, that would permit of their differential staining while all their structures were fairly normal in size and shape. Any such method must, of course, fail both in the temporary preservation of the soluble elements of the tissue and in the permanent preservation of any of the tissue unless there is subsequent "fixation" (that is, coagulation of the proteins). Yet such a method may give not only quickly obtainable pictures of the normal size, shape, and arrangement of the cells, but also important details of the normal internal structure of cells, supplementing, and in some instances correcting, our concepts obtained from the study of fixed tissues.

Ten years ago, in seeking some means of rapidly staining pathologic specimens as they came from the operating room that a diagnosis might be given while the patient was still on the table, to guide the surgeon in his further operative procedure, I worked out, from the basis of Bethe's methylene-blue intravital staining, a method which has since proved very satisfactory. It has been published twice before,⁸ but it may not be amiss to reproduce it here for the sake of those not familiar with it.

DETAILS OF METHOD OF STAINING

1. Freeze bits of fresh tissue, not more than 2 by 10 by 10 mm., in dextrin solution and cut sections 5 to 15 microns thick.
2. Remove the sections from the knife with the tip of the finger and allow them to thaw thereon.
3. Unroll the sections with a camel's-hair brush or glass lifter in 1 per cent. sodium chlorid solution.

4. Stain ten to twenty seconds in Unna's polychrome methylene-blue.

5. Wash out momentarily in fresh 1 per cent. sodium chlorid solution.

6. Mount in Bruns' glucose medium.

The tissue must be fresh, that is, the cells must be still alive, and hence present no cytolytic changes. Almost all tissues which we examine have been removed from the body not more than five minutes, and usually not more than two minutes before they are frozen. However, we have gotten fair preparations in some instances from tissues that have been from one to two hours out of the body. If kept in the ice-chest under proper conditions, they may be stained after a still longer period. *Most failures are due to the fact that the cells are dead before the tissues are frozen.*

The dextrin solution is prepared by stirring dry dextrin into boiling water until the mixture is about the consistence of commercial maple syrup. Five-tenths per cent. of phenol may be added in warm weather.

The ether freezing microtome is an unsatisfactory makeshift. Now, that tanks of carbon dioxid may be procured in every town which has a soda fountain, there is no longer any excuse for the use of the ether instrument. The microtome should be a well-made machine, capable of cutting to five microns, though sections of many tissues cannot be handled quite so thin. In our experience, the best instrument for the purpose is the Spencer Automatic, though good results may also be obtained with the Sartorius, the Leitz, and the new Bausch and Lomb instruments with mechanical knife carriers. A freezing microtome which is in constant service in a laboratory in connection with a surgical clinic receives hard usage, and its parts therefore must be strong and well made. The valve for controlling the gas is apt to become quickly worn and leaky. This valve is more convenient if placed at the microtome and not at the tank. It should have a long, flat, T-shaped handle for ease of operation. Whatever style of microtome is used, the metal plate on which the tissue is frozen should be insulated in some manner from the metal parts of the remainder of the ap-

paratus. This prevents the heat being transferred between the two, makes less gas necessary, and keeps the tissue frozen longer.

The carbon dioxid tank should be suspended on metal hooks or brackets underneath the table on which the microtome is placed. Thus, the small amount of dirty water which is present in many tanks will not find its way into and clog the valve of the freezing chamber, as it is apt to do when the gas tank is placed in a vertical position above the work-table.

In freezing, the gas should not be turned on in a large stream and allowed to flow until the tissue is frozen. Much gas can be saved and much more satisfactory preparations made if it is turned on in intermittent spurts, giving time for the tissue to freeze more slowly, and thus more evenly throughout. It should not be frozen more solidly than is necessary for cutting. When this occurs, however, the upper layer may be thawed slightly by placing the finger on the tissue.

The sections should be cut by rapidly repeated strokes, not permitting the surface of the tissue to thaw after each cut. A half dozen or more should be cut, and the first ones rejected, insuring sections of even and uniform thickness.

In trimming out blocks of tissue for freezing, the pieces of tissue should be not more than 2 mm. in thickness, and the transverse diameter should be as small as is possible and still include the desired field of examination. The smaller the block down to 2 mm., the better the sections, and the more easily they may be handled. In general the blocks should be so trimmed that the sections when cut will be rectangular or rounded, rather than triangular in outline. Unless the block is more than 1 cm. in transverse diameter, the long edge should be so placed on the freezing plate that the knife-edge will strike it parallel. Where blocks are more than 1 cm. in transverse diameter, a shorter edge may be placed so as to first come in contact with the knife. When very minute bits of tissue are to be frozen, it is best to partially freeze a small amount of dextrin solution first, and then place the tissue on top of it, thus keeping it 1 mm. or more away from the metal freezing plate and avoiding contact of the knife therewith.

The knife-edge must be as sharp as it is possible to make it. The blade should be very rigid, preferably wedge-shaped, and not hollow-ground. We have attempted to use safety-razor blades in special holders, but have found them to vibrate altogether too much. Several blades, not less than four, should be provided for each microtome, since the edges are dulled very quickly with the best of tissues, and routine blocks are apt to contain unsuspected calcified areas. Reserve cylinders of carbon dioxide should also be kept in some nearby cool place, so that they may be changed rapidly if necessary.

When sections are removed from the knife with the tip of the finger and allowed to thaw thereon, a process which may be hastened by breathing on them, air-bubbles are less apt to form than if they are removed with a brush and placed immediately in salt solution. As the sections go into the salt solution, they are usually more or less rolled up, and must be straightened out by gentle manipulation by moving them up and down either with a small camel's-hair brush or with a bent glass lifter with a dull point. This is best done in a clear glass dish over a black background, permitting the unstained sections to be readily seen.

When the sections have been straightened out, they should be caught under the middle with a small bent glass rod lifter and transferred to the stain. If, in the stain, a direct up-and-down motion is made with the lifter, the section will remain thereon, the folded portions merely "flapping" in the stain. Occasionally a section will be lost off the lifter. If the receptacle holding the stain is large, much time may be lost and the section injured in finding it. This may be obviated to a considerable extent by using a very small receptacle, of not more than 10 c.c. capacity, with a rounded bottom. Small individual glass salt-cells and the small porcelain teacups from a set of doll's dishes are quite convenient. The bent portion of the glass lifter should be less than $1\frac{1}{4}$ cm. long and the end should be rounded in the flame.

We have never yet gotten an unsatisfactory lot of Unna's polychrome methylene-blue direct from Gröbler, while at the same time

we have gotten one or more unsatisfactory specimens from every other dealer from whom we have purchased, even when the stain was said to have been made by Grübler and rebottled by the selling firm. Now that the German supply is temporarily cut off, we are making our own. The secret of success seems to be in taking a large quantity of Unna's alkaline methylene-blue (methylene-blue 1; carbonate of potassium, 1; water, 100) and allowing it to ripen for from six months to a year with the largest surface possible exposed to the air in a flask stoppered only with cotton. When the stain is properly ripened, it contains a considerable portion of methylene red, and should give sharply differentiated dark blue, purple, and pinkish red color-contrasts with fresh tissue. The stain, even in 5 or 10 c.c. amounts, may be used over and over again, but should be discarded when it shows a precipitate or when it no longer gives sharp color-contrasts.

The sodium chlorid solution, which is used for washing out the gross excess of stain, should be contained in a white porcelain dish, or if in a clear glass receptacle, this should be over a white surface. In this manner the evenness of staining and the general appearance of the sections may be more readily seen.

Bruns' glucose medium is prepared as follows: Distilled water, 140 c.c.; camphorated spirit, 10 c.c.; glucose, 40 gm.; glycerin, 10 c.c.

Mix the hot water, glucose, and glycerin thoroughly, add the spirit, shake and filter to remove the excess of camphor which is precipitated on mixing. The solution should be kept in relatively small stoppered bottles. In warm weather a crystal of thymol may be added to prevent the growth of molds. The solution is cheap, and should be thrown away as soon as it becomes colored with dye.

Sections are most conveniently spread out and transferred to the slide if the solution is contained in a long narrow porcelain dish about 1 inch deep by $1\frac{1}{4}$ by 4 inches. These may be obtained in the market as white porcelain match-trays.

The section should be moved about in the glucose medium for a few seconds, not only to straighten it out but also to obtain better

differentiation. The end of the glass slide is then slipped under it, the edge of the section held to the slide by the lifter, and the whole preparation raised out of the solution. The excess of glucose medium is wiped off from underneath the slide and around the section, the cover dropped on, and the preparation is ready for the microscope.

All the steps of the process may be carried out in one minute from the time the tissue is placed on the freezing plate of the microtome until the slide is placed on the stage of the microscope. Various tissue elements should be thoroughly contrasted in pink, red, purple, and dark blue. Mitotic figures, when present, are beautifully shown. Many bacteria are stained.

The method, as given above, has been used for diagnostic purposes and for the study of fresh tissues in the laboratories of the Mayo Clinic for more than ten years. During that period it has been frequently modified by members of the laboratory staff. All such modifications, however, have been abandoned and the original method returned to. Probably the most useful modification is one which we used several years ago, and which has subsequently been independently developed and published by Pierce.⁹ This consists in the substitution of distilled water for the sodium chlorid solution, and of carbolthionin for the polychrome methylene-blue stain. The carbolthionin stain may be more quickly prepared than the polychrome methylene-blue, and is perhaps more stable. Bacteria are stained by it a little more sharply than by polychrome methylene-blue. However, sections must not be left overlong in the stain, which contains $2\frac{1}{2}$ per cent. phenol.

Sections stained by the polychrome methylene-blue method remain in excellent shape for two or three hours after the tissue has been removed from the body, and may be in fairly good condition, if kept cool, for a day or two. No satisfactory method has as yet been devised whereby desirable sections can be fixed and preserved after staining in this manner. Success in this direction probably lies along the lines indicated in Bethe's original method for the fixation of tissues vitally stained by injections of methylene-blue.

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A DEVICE FOR HOLDING SOLUTION BOTTLES IN OPERATING ROOMS *

DONALD C. BALFOUR

Each bottle shown in the accompanying photographs has as its feature a combination handle and corking device which can easily be detached from the bottle and sterilized. The chief advantage, therefore, is that the handle, being sterile, the surgeon



Fig. 218.—Method of attaching stoppers.

or assistant may readily obtain more iodine before or during an operation without the soiling of gloves. To those using the benzine, iodine and alcohol method of skin preparation, for which the apparatus is especially adapted, other points of advantage are quite

* Reprinted from Jour. Amer. Med. Assoc., 1915, lxiv, 584.

obvious, for instance, evaporation is prevented (the handle being equipped with a spring), solutions are not wasted, bottles are not



Fig. 219.—Stoppers in place and bottles in use.

broken, and time and trouble are saved the operating-room personnel.

A SIMPLE OPERATING MALLET

HENRY W. MEYERDING

In surgery of the bone it is important to be able to watch the cutting edge of the chisel, and accurately to gage the force of the blow without danger of striking the hand and tearing the glove. The mallet of my design here illustrated has been used with satisfaction for several years in the Mayo Clinic. It is an alloy of zinc,



Fig. 220.—Operating mallet.

copper, and aluminum so composed that the metallic ring of the hammer is avoided, so shaped as to allow a firm grip, and heavy enough to deliver a forceful blow. It measures 8 inches in length, and the diameters are $2\frac{1}{2}$ inches at the head and $1\frac{1}{4}$ inches at the handle.

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DESCRIPTION OF A SELF-RETAINING BLADDER RETRACTOR.*

JAMES C. MASSON

In all surgical operations on the bladder good exposure is a very important factor, and to accomplish this a great many instruments have been devised. In our experience the lateral retractors of the Walker type have been the most practical; but they have the ob-



Fig. 221.—Instrument ready to insert.

jection of requiring extra assistants. To avoid this we have applied the same type of blades to a self-retaining retractor. When the instrument is closed, the upper parts of the blades dovetail into one another to help in inserting. They are attached to the rest of the retractor by pivot-joints, allowing free movement, which is a great convenience, as the body of the retractor can be turned to

* Reprinted from Surg., Gyn. and Obst., 1916, xxii, 357.

where it is least in the way of the operator. By spreading the retractor and holding the fundus well back with a long tongue-depressor in the hand of an assistant, the operator can see the



Fig. 222.—Instrument in place.

entire interior of the bladder. The retractor is especially useful for exposure in removing neoplasms of the bladder and in suturing the capsule following the removal of adenomatous hypertrophy of the prostate (Figs. 221 and 222).

GENERAL PAPERS

SHOCK AND HEMORRHAGE: AN EXPERIMENTAL STUDY*

FRANK C. MANN

The experimental study of the phenomenon termed "surgical shock" is difficult because what constitutes shock has never been very clearly defined. This has led to many conflicting data and diverse theories. It is necessary, therefore, to define carefully what is meant by "surgical shock" and to prescribe the limits of its clinical application.

In a previous article¹ I have outlined the experimental conditions under which could be made a study of the syndrome of post-operative shock. In order to give definite value to the work, two factors have been closely observed: (1) A uniform method of producing shock; and (2) the reduction of the animal to the condition of shock as defined in my previous study of the subject; *i. e.*: (a) great loss of sensibility; (b) pallor of mucous membranes; (c) small, weak pulse; (d) irregular, rapid, shallow, or gasping respiration; and (e) materially lowered blood-pressure.

In regard to the first factor, I have pointed out the impracticability of attempting to produce, by traumatizing nerve-trunks, joints, etc., the condition in which the clinical signs of shock are present. The only uniform method of producing shock experimentally is to open the abdomen and expose the viscera. It is obvious that only the condition known as post-operative shock can be the subject of experimental investigation. Psychic shock and the use of the term as applied to railway accidents are not subjects for experimental observation, and it is futile to seek a common cause for all these varied manifestations.

* Reprinted from Surg., Gyn. and Obst., 1915, xxi, 430-441.

All my data on shock have been secured from experiments on animals in which the clinical signs, as enumerated, appeared when the viscera were exposed. These results are comparable with those obtained by other experimental observers inasmuch as most observers have produced shock by visceral traumatization. Clinically my results may be applied to the shock produced during operation.

It is generally conceded by clinical and experimental investigators that shock is in some manner associated with circulatory failure, due either to a cardiac or vasomotor impairment. In either case overstimulation of the nervous system has been considered the cause of this profound depression of the circulation. Numerous experiments have established the fact that the heart is not primarily impaired in shock, but is able to do its work efficiently if enough blood is returned to it. It has been almost as conclusively proved that the vasomotor center is not fatigued or exhausted. On the contrary, this center is probably in a state of hyperirritability until the condition is moribund and is vainly striving to maintain blood-pressure at its normal level.

Henderson² has pointed out that stagnation of the circulation does not necessarily mean cardiac or vasomotor failure. He emphasizes the fact that it is the function of the heart to pump and the function of the vasomotor system to regulate peripheral resistance. Given a sufficient amount of blood, equilibrium is preserved, and these two factors are able to maintain a normal blood-pressure. However, at a point of its cycle distal to the arterioles in the capillaries and venous reservoirs, the blood encounters a place where it is more or less beyond the control of the heart and vasomotor system, and another factor becomes essential to the maintenance of effective circulation: a mechanism which will return the blood from the capillaries to the heart. An impairment of some part of this mechanism can produce a failure of circulation despite an effective pump and vasomotor system. Henderson believes this mechanism to be injured in shock by loss of carbon dioxid. This causes the walls of the veins to lose tone and the tissues to undergo changes whereby they imbibe more water

from the blood and thus diminish the amount of circulating fluid.

As the result of a previous investigation I concluded that shock produced by the exposure of the abdominal viscera was due to a loss of circulatory fluid, the causes for this loss probably being the same as those producing the stasis which pathologists consider as part of the process of inflammation.

The problem at hand was to determine whether there is in shock an actual loss of circulating fluid, and, if so, whether the loss can be accounted for simply by vasomotor failure. In a measure the problem has been solved by Lyon and Swarts,³ who found that the percentage of blood was decreased in all organs after shock.

The amount of blood that can be obtained from a large arterial trunk—as the femoral—is the measure of efficient blood; it is the amount which can be returned to the heart and lungs and, after aëration, be pumped out to feed the tissues. The blood which can be secured from the venous side of the circulatory system—as from the right auricle—is the amount that is freely movable, but was not returned to the arterial system. Their sum is the amount of mobile blood in the body. This sum subtracted from the total amount of blood gives the quantity of immobilized blood; the fixed quantity in the tissues. So far as the immediate circulatory needs of the organism are concerned, this latter amount of blood is useless.

In my experiments the total amount of blood was estimated in its relation to the body weight. The percentage used was 7.7 per cent., or one-thirteenth of the total weight of the animal. This standard is open to a certain degree of error, particularly since it was impossible to obtain enough dogs of approximately the same size and breed. However, this source of error was reduced to a minimum by using in each series the same type of animals in the same physical condition and, as the study is of comparative conditions, the variation does not materially affect averages.

The general technic was uniform in all the experiments. The animal, which had been fasted for eighteen hours, was etherized

TABLE I

EXPERIMENTS	NUMBER OF EXPERIMENTS	BODY WEIGHT OF ANIMAL	WEIGHT OF BLOOD OBTAINED FROM RIGHT AURICLE, FEMORAL ARTERY AND CAVA	WEIGHT OF BLOOD OBTAINED FROM RIGHT AURICLE AND CAVA	TOTAL AMOUNT OF BLOOD OBTAINED	ESTIMATED TOTAL AMOUNT OF BLOOD ON THE BASIS OF 7.7 PER CENT. OF BODY WEIGHT	AMOUNT OF BLOOD LEFT IN TISSUES	PERCENT-AGE OF BLOOD OBTAINED FROM FEMORAL ARTERY	PERCENT-AGE OF BLOOD OBTAINED FROM RIGHT AURICLE	TOTAL PERCENT-AGE OF BLOOD OBTAINED	PERCENT-AGE LEFT IN TISSUE	NORMAL BLOOD-PRESSURE	BLOOD-PRESSURE AT TIME OF EMERGENCE
Series of normal animals	3	9,952	506	60	566	766	200	66	8	74	26	125	125
	4	11,000	600	95	695	847	132	71	11	82	18	120	120
	5	10,450	600	100	700	804	134	70	12	83	17	130	125
	13	9,330	476	60	536	718	182	66	8	75	25	145	145
	15	13,933	685	105	790	1,072	232	64	10	74	26	130	130
	33	8,708	400	70	470	670	200	60	10	70	30	150	150
Average													
Series in which the cervical cord was sectioned	7	9,071	345	85	430	608	268	40	12	62	38	150	100
	8	10,947	400	90	490	842	352	47	11	58	42	125	65
	9	24,383	990	195	1,185	1,876	691	54	10	64	36	150	100
	11	11,072	550	100	650	852	202	65	12	76	24	145	100
	12	9,206	580	95	475	708	223	54	12	66	34	155	75
	35	13,425	600	120	720	1,083	313	58	12	70	30	140	78
Average													
Series in which ether was pushed until respiratory failure	10	22,890	700	210	910	1,761	851	40	12	52	48	130	0
	14	15,923	660	130	790	1,225	311	53	11	64	36	120	0
	17	14,928	475	160	635	1,148	513	42	14	55	45	130	10
	26	16,918	625	200	825	1,501	476	48	15	63	37	128	0
	27	15,177	575	155	730	1,167	437	48	13	62	38	102	0
	34	4,353	150	42	192	335	143	45	13	57	43	120	5
Average													
Average													

Series in which shock was produced by exposure of the abdominal viscera	6	8,459	176	74	250	651	401	27	11	38	62	147	40
	18	10,947	260	90	350	842	492	31	11	42	58	122	70
	20	6,220	145	55	200	478	278	30	11	42	58	124	50
	24	10,201	250	85	335	785	350	32	11	43	57	108	50
	28	7,962	150	75	225	612	387	24	12	37	63	105	50
	36	13,933	250	105	365	1,072	707	23	11	34	66	140	70
Average.....													
Experiments in which the viscera were exposed but complete shock was not allowed to develop	19	13,186	390	95	485	1,014	529	38	9	48	52	150	90
	23	7,713	215	85	300	592	293	36	14	51	49	105	65
Experiment in which the splanchnic nerves had been sectioned just above diaphragm seven days previously	21	12,938	475	150	625	995	370	49	15	64	36	134	130
Experiment in which the spinal cord from sixth cervical segment peripherally was completely destroyed	25	7,464	250	85	335	574	239	42	15	57	43	120	0
Experiment in which, after producing shock, blood-pressure was increased by injection of adrenalin	29	5,971	175	35	210	459	249	38	8	46	54	110	180
Experiment in which the vasomotor center was tested after hemorrhage	30	10,450	(1)295 (2)200	130	625	804	123	62	16	78	22	95	(1)150 (2)45

TABLE I.—(Continued)

EXPERIMENTS	NUM- BER OF EXPERI- MENTS	BODY WEIGHT OF ANIMAL	WEIGHT OF BLOOD OBTAIN- ED FROM RIGHT FEM- ORAL ARTERY	WEIGHT OF BLOOD OBTAINED FROM RIGHT AURICLE AND CAVA	TOTAL AMOUNT OF BLOOD OBTAINED	ESTIMATED TOTAL AMOUNT OF BLOOD ON THE BASIS OF 7.7 PER CENT. OF BODY WEIGHT	AMOUNT OF BLOOD LEFT IN TISSUES	PERCENT- AGE OF BLOOD OBTAINED FROM FEMORAL ARTERY	PERCENT- AGE OF BLOOD OBTAINED FROM RIGHT AURICLE	TOTAL PERCENT- AGE OF BLOOD OBTAINED	PER- CENT- AGE LEFT IN TISSUE	NORMAL BLOOD- PRESS- URE	BLOOD- PRESSURE AT TIME OF HEMO- RHAGE
Experiment in which curare was given until respiration had almost ceased	31	21,521	1,000	335	1,335	1,655	320	60	20	81	19	140	158
Experiment in which abdomen was widely opened just before bleeding	37	7,091	430	40	470	545	75	79	7	86	14	115	125
Experiment in which the bleeding was preceded by a slow hemorrhage of 36 per cent. of the ani- mal's blood	38	83,948	(1)275 (2)140	50	465	641	176	65	8	73	28	130	45
Experiment in which the cervical cord was sectioned two hours before bleed- ing	41	16,918	675	145	820	1,301	481	52	11	63	37	145	75

and carefully weighed. The anesthesia was maintained by the autointratracheal inhalation method.⁴ Blood-pressure was taken from the right carotid artery. A cannula was placed in the right femoral artery. After performing the experimental procedure, such as producing shock, sectioning the spinal cord, etc., the femoral artery was opened and all the blood that could be secured was obtained. The thorax was then opened, the pericardium stripped over the heart, and, turning the animal on its side in a slight Trendelenburg position, the right auricle and, later, the cava were opened, allowing the blood to flow into a wide-mouthed receiver. The exact weight of the separate specimens was recorded.

The observations fall into four different groups: (1) In the first series normal dogs were used as controls to determine how much blood could be obtained by the method described; (2) in the second series the cervical cord was cut before bleeding; (3) in the third series the animals were practically killed with ether and the bleeding was done after the institution of artificial respiration; (4) in the fourth series the animals were shocked by exposure of the abdominal viscera. Several special experiments devised to emphasize certain points are also reported. (Table I, Detailed Observations; Table II, Condensed Data.)

TABLE II

EXPERIMENTS	PERCENTAGE OBTAINED FROM FEMORAL ARTERY	PERCENTAGE OBTAINED FROM RIGHT AURICLE AND CAVA	TOTAL PERCENTAGE OBTAINED	PERCENTAGE LEFT IN THE TISSUE
Series of normal animals.....	66	10	76	24
Series in which the cervical cord was sectioned.....	54	11	69	34
Series in which ether was pushed until respiratory failure.....	46	13	59	41
Series in which shock was pro- duced by exposure of abdominal viscera.....	28	11	39	61
Experiment in which the spinal cord from sixth cervical seg- ment peripherally was destroyed	42	15	57	43
Experiment in which, after the pro- duction of shock, adrenalin was given and the animal bled when blood-pressure had reached its highest point.....	38	8	46	54

In the first series the blood-pressure was taken with the normal animal in a moderate depth of etherization, and then the bleeding from the femoral artery was started. From these animals we

obtained an average of 66 per cent. of the blood from the femoral artery, 10 per cent. from the heart, making a total of 76 per cent. obtained, and leaving 24 per cent. in the tissues. These results are a fair average for the experimental conditions under which they were secured and form the standard of comparison for the results of all the other experiments.

Experiment 13.—March 6, 1915. Dog; rather poor brindle bull; weight, 9330 gm. The animal was etherized; carotid blood-pressure taken and a cannula placed in the right femoral artery. Normal blood-pressure, 145. From the femoral artery, 476 gm. of blood were obtained and 60 gm. from the right auricle. The estimated total amount of blood was 717 gm. From the femoral artery 66.3 per cent. was recovered, and 8.3 per cent. from the heart, making a total of 75 per cent. obtained, and leaving 25 per cent. of the blood in the tissues (Fig. 223).

In the second series the cervical cord, usually the sixth or seventh segment, was sectioned before the bleeding. As this severs

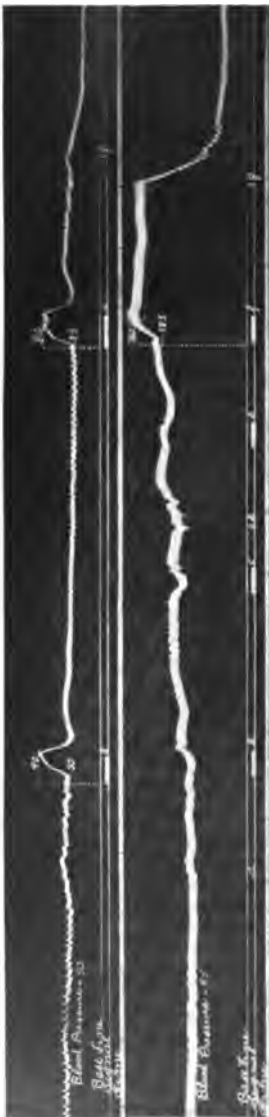


Fig. 223 (*Experiment 13*).—Normal blood-pressure, 95. Right and left vagus sectioned at *a* and *d* respectively. At *b*, *c*, *e*, and *h* central end of right vagus stimulated. Central end of left vagus stimulated at *f* and *i*. At *g* the animal was bled 37 per cent. of its blood. At *j* it was bled to death. Note the reaction of vasomotor center after hemorrhage.

practically all the vasoconstrictor fibers from their connection with the medullary center, the procedure simulates as nearly as possible a total paralysis of the medullary vasomotor center. The fall in blood-pressure induced by this operation approached that observed in shock in but a minority of cases. It should be borne in mind that even with the most careful hemostasis some blood was lost during the operation. The blood-pressure was allowed to reach a constant level before the bleeding was started. From these animals an average of 55 per cent. of blood was obtained from the femoral artery and 11 per cent. from the heart, making a total of 66 per cent. recovered, and leaving 34 per cent. in the tissues. It is thus seen that after removal of the influence of the medullary vasomotor center an increase of 10 per cent. of blood remained in the tissues. The following protocol is a good example of this series:

Experiment 9.—March 5, 1915.
Dog; brown and white male mongrel; weight, 24,383 gm.

9.45 A. M.: Etherized; carotid blood-pressure taken; cannula placed in femoral artery. 9.55 A. M.: Pulse, 158; respiration, 36; blood-pressure, 150. 10.07 A. M.: Incision made for exposing spinal cord. 10.27 A. M.: Cord sectioned (seventh cervical segment); blood-pressure fell to 100. 10.40 A. M.; Bled from the femoral, obtaining 990 gm. of blood; 195 gm. obtained from the heart. The esti-



Fig. 284 (*Experiment 11*).—Normal blood-pressure, 145. Marked fall in pressure when ligature was passed around cord. After section of sixth cervical segment blood-pressure remained at 100; 65 per cent. of blood secured from femoral artery and 12 from heart.

mated amount of blood was 1875 gm.; 54 per cent. was obtained from the artery and 10 per cent. from the heart, making a total of 64, and leaving 36 per cent. in the tissues.

In order to test the effect that blood-pressure might have upon the quantity of blood obtained, a complete failure of respiration and a more or less complete vasomotor paralysis by overetherization were produced in a third series of experiments. After taking the normal blood-pressure in these animals, ether was pushed to the point of respiratory failure. When the blood-pressure had practically reached zero and no pulsation could be felt in the femoral artery, artificial respiration was instituted by means of alternate thoracic and abdominal compression and the bleeding was started. Spontaneous respiratory movements returned in but one experiment, and in this case they were of the convulsive type. It usually required about twice as long to obtain all the blood in animals of this series as in the controls. I was very much surprised to find that under such conditions an average of 46 per cent. of blood could be obtained from the femoral artery, 13 per cent. from the heart, leaving 41 per cent. in the tissues. In these animals there was an average increase of 17 per cent. of blood left in the tissues as compared with the amount in normal animals. Experiment 26 is a typical experiment:

Experiment 26.—March 11, 1915. Dog; male shepherd; weight, 16,918 gm.

3.40 P. M.: Etherized. Apparatus arranged to record carotid blood-pressure. Cannula placed in right femoral artery. 3.50 P. M.: Pulse, 140; respiration, 22; blood-pressure, 128. 3.52 P. M.: Began to push ether. 3.56 P. M.: Respiration failed. 3.59 P. M.: Blood-pressure reached zero; no pulsation in femoral artery. Femoral artery opened; thoracic and abdominal compression started. From the right femoral artery 625 gm. of blood were secured, 200 gm. from the heart. The estimated amount of blood was 1301 gm. This makes 48 per cent. from the artery, 15 per cent. from the heart, a total of 53 per cent., leaving 37 per cent. in the tissues (Fig. 225).

In the fourth series of experiments, after obtaining the normal blood-pressure, the right vagus was sectioned and the central end

stimulated for the purpose of testing the response of the vasomotor center to reflex stimulation. Two such tests of the vasomotor center were made before the abdomen was widely opened and the viscera exposed. When the resulting condition fulfilled all the clinical requirements for shock, the response of the vasomotor center was tested a third time. In every case the response was practically the same in the shocked condition as in the control. After this procedure the animal was bled. None of these experiments produced a very low blood-pressure, and the reaction of the vasomotor center was normal. An average of only 28 per cent. of blood was obtained from the femoral artery, 11 per cent. from the heart, making a total of 39 per cent. obtained, leaving 61 per cent.

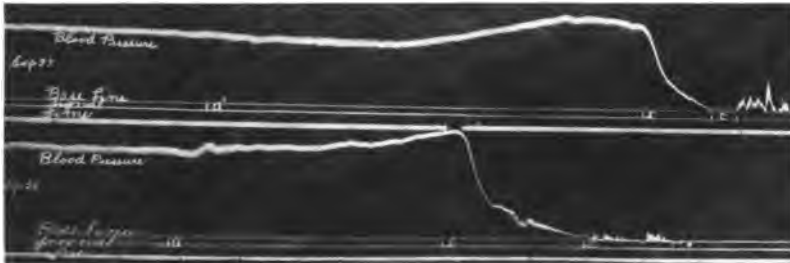


Fig. 225 (*Experiment 26*).—Normal blood-pressure, 128. Began to push ether at *a*. Respiration failed at *b*. Femoral artery was opened and artificial respiration started at *c*. Obtained 48 per cent. of blood from artery and 15 from heart. (*Experiment 27*.) Normal blood-pressure, 102. Signals *a'*, *b'*, and *c'* signify same as in *Experiment 26*. Obtained 48 per cent. of blood from artery and 13 from heart.

in the tissues. This means that in these animals less than 40 per cent. of the blood was available and that almost 37 per cent. more than the normal amount was stagnated in the tissues. Such a loss of circulating fluid is sufficient to produce all the accompanying clinical signs of shock. *Experiment 18* is typical:

Experiment 18.—March 8, 1915. Dog; weight, 10,947 gm. 9.45 A. M.: Etherized. Apparatus arranged to record carotid pressure and to bleed from femoral artery. Right vagus exposed. 9.15 A. M.: Pulse, 130; respiration, 42; blood-pressure, 122. 9.18 A. M.: Sectioned right vagus. Slight rise in blood-pressure. 9.43 A. M.: Stimulated central end right vagus for ten seconds. Blood-pressure increased 30. 9.45 A. M.: Stimulated central end

right vagus. Blood-pressure increased 55. 9.50 A. M.: Abdomen opened and viscera exposed; blood-pressure gradually fell. 1 P. M.: Animal has all the signs of shock. Has had no ether since 12.05; eye reflex positive; pulse, 122, weak; respiration, 18, gasping; blood-pressure, 70. 1.01 P. M.: Stimulated central end right vagus ten seconds. Blood-pressure increased 36. 1.04 P. M.: Stimulated central end of vagus twenty seconds. Blood-pressure increased 40. 1.05 P. M.: Blood-pressure, 70. Bled from femoral artery 260 gm. and 90 gm. from the heart. Estimated amount of blood was 842; 31 per cent. was recovered from artery, 11 from the heart, making a total of 42 per cent., and leaving 58 per cent. in the tissues (Fig. 226).

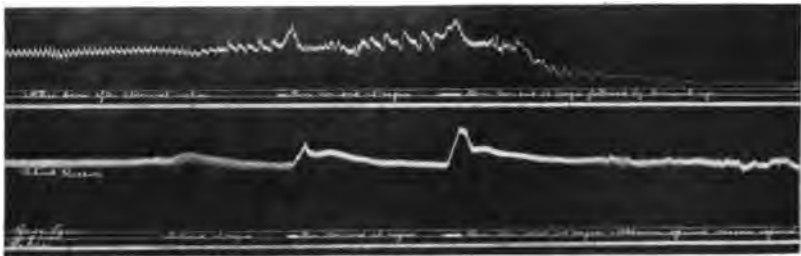


Fig. 226 (*Experiment 18*).—Normal blood-pressure, 122. After exposing viscera for three hours it had decreased to 70. Reaction of vasomotor center practically normal. Obtained 31 per cent. of blood from artery and 11 from heart.

These experiments seem to prove that the reason for the common symptoms of shock and hemorrhage is that they have a common pathology. In shock a large percentage of blood is as effectually lost from the circulation as if it had escaped by a free hemorrhage. That this decrease in the amount of circulating blood is essentially different from the venous congestion produced by paralysis of the medullary vasomotor center is shown by a comparison between the amount of blood left in the tissues after section of the cervical cord and that after the production of shock. In the former condition there is only 10 per cent. more blood left in the tissues than in the control, while in the latter there is a surplus of 37 per cent. stagnated in the tissues.

However, these experiments do not preclude the possibility of the production of splanchnic paralysis by an inhibition of the

cord-centers, as held by Janeway and Ewing.⁵ While it is true that vasomotor reflexes involving the cord-centers take place during shock, the following experiments show that the centers are not fatigued and that complete vasomotor paralysis does not produce immobilization of the blood. That the centers are active was shown by Experiment 125:

Experiment 125.—February 20, 1914. Cat, female. Etherized. Blood-pressure, 98. Dorsal cord exposed and first segment sectioned; blood-pressure fell until it reached a constant level of 70. Abdomen was then opened and viscera exposed. Blood-pressure fell rather quickly to 42. When blood-pressure was 14 and the animal in marked shock, a small probe was passed peripherally in the spinal canal, compressing the cord. Blood-pressure quickly increased to 52.

That total destruction of the central vasomotor system does not produce the immobilization of the blood found in shock is shown by the following experiment:

Experiment 25.—March 11, 1915. Dog; small brown female cur; weight, 7464 gm.

8.50 A. M.: Etherized. Apparatus arranged to record carotid blood-pressure and a cannula placed in the femoral artery. 9 A. M.: Pulse, 150; respiration, 20; blood-pressure, 120. 9.05 A. M.: Incision made to expose cervical cord. Cord laid bare; slight hemorrhage. 9.20 A. M.: Ligature passed around cord. 9.22 A. M.: Cord sectioned at sixth cervical segment; blood-pressure, 94. 9.35 A. M.: Cord exposed in lower lumbar region. 9.50 A. M.: Probe passed from cervical opening peripherally. Some little difficulty was experienced in keeping probe in canal. However, the entire cord was finally destroyed from cervical opening to lumbar opening. There was some hemorrhage. At first the blood-pressure was not markedly affected, but the respiration became irregular and the blood-pressure finally fell to zero. 10.20 A. M.: Animal bled. Secured 250 gm. of blood from femoral artery and 85 gm. from heart. The estimated amount of blood was 574 gm.; 42 per cent. was obtained from the artery, 15 per cent. from the heart, making a total of 57 per cent. and leaving 43 per cent. in the tissues.

That loss of vasomotor tone with splanchnic congestion for the length of time necessary to produce shock does not give rise to identical conditions is shown by Experiment 41:

Experiment 41.—March 29, 1915. Dog, male shepherd; weight, 16,918 gm. 8.45 A. M.: Etherized. Apparatus arranged to record carotid blood-pressure. Cannula placed in femoral artery. 9.04 A. M.: Blood-pressure, 145. 9.06 A. M.: Incision made to expose cervical cord. 9.12 A. M.: Passed ligature around cord. 9.18 A. M.: Cord sectioned at sixth cervical segment; slight hemorrhage. Blood-pressure fell to 60. Animal was kept lightly etherized until 11.50. Blood-pressure at this time was 75. Femoral artery was opened, obtaining 675 gm. of blood; 145 gm. were obtained from the heart. The estimated amount of blood was

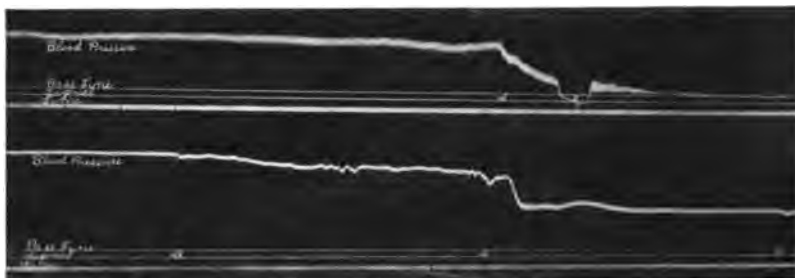


Fig. 227 (*Experiment 41*).—Normal blood-pressure, 145. Cervical cord exposed between *a* and *b*. Fall in blood-pressure due to passing ligature around cord. Cord sectioned at sixth cervical segment at *c*. Blood-pressure fell to 60, but after 2.5 hours increased to 75, when the femoral artery was opened (*d*). Obtained 52 per cent. of blood from artery and 11 from heart.

1301 gm.; 52 per cent. was secured from artery and 11 per cent. from the heart, making a total of 63 per cent., and leaving 37 per cent. in the tissues. This is practically the same result as in the cord series (Fig. 227).

The following experiment shows that the immobilization of the blood in shock takes place beyond the control of the vasomotor system. This experiment also emphasizes the fact that the amount of blood obtained is not primarily dependent upon blood-pressure.

Experiment 29.—March 12, 1915. Dog, young brown female spaniel. Weight, 5971 gm. 2.50 P. M.: Etherized. Carotid

blood-pressure taken. Cannula placed in right femoral artery; left femoral vein exposed. 3 P. M.: Pulse, 132; respiration, 18; blood-pressure, 110. 3.13 P. M.: Abdomen opened; viscera exposed. Marked fall of blood-pressure, which quickly recovered and was followed by a gradual fall. 4.20 P. M.: Animal in moderate degree of shock; has needed no ether since 4. Eye reflex positive; blood-pressure, 50. 4.23 P. M.: Injected 2 c.c. of adrenalin (1:1000) into femoral vein; blood-pressure increased from 50 to 180. 4.24 P. M.: When blood-pressure had reached highest point, the femoral artery was opened. Obtained 175 gm. of blood from artery, 35 gm. from the heart. The estimated amount of blood was 459 gm., of which 38 per cent. was secured from the artery and 8 per cent. from the heart, making a total of 46 per cent.,

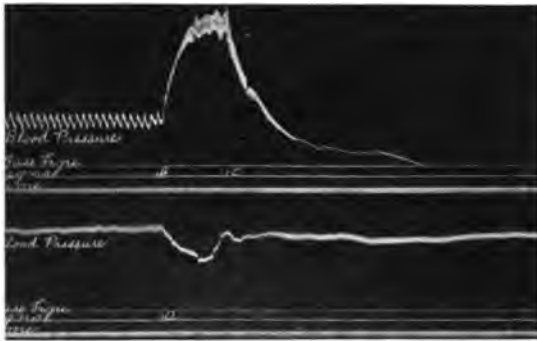


Fig. 228 (*Experiment 29*).—Normal blood-pressure, 110. Abdomen opened at *a*. When animal was in shock, with blood-pressure of 50, 2 c.c. adrenalin was injected (*b*). Femoral artery opened at *c*. Obtained 38 per cent. from artery and 8 from heart.

leaving 54 per cent. in the tissues. The maximum constriction of the arterioles in shock with an increase of blood-pressure far above normal did not materially increase the amount of mobile blood as compared with the average of the shock series (Fig. 228).

The following experiments show that considerable blood can be lost in both shock and hemorrhage and still a relatively high blood-pressure be maintained. The parallelism of the two conditions and the activity of the vasomotor system are again presented.

Experiment 30.—March 13, 1915. Dog, black, white, and yellow female mongrel; weight, 10,450 gm. 9.15 A. M.: Etherized.

Apparatus arranged to record carotid blood-pressure and to bleed from femoral artery. Both vagi exposed. 9.30 A. M.: Pulse 170; respiration, 26; blood-pressure, 95. 9.34 A. M.: Right vagus cut; slight rise in blood-pressure. 9.35 A. M.: Stimulated central end right vagus; respiration ceased; slight rise in blood-pressure. 9.38 A. M.: Repeated stimulation; same result. 9.40 A. M.: Sectioned left vagus. 9.41 A. M.: Stimulated central end right vagus; slight increase in blood-pressure. 9.42 A. M.: Stimulated central end of left vagus; blood-pressure increased 35. 9.44 A. M.: Blood-pressure, 150. Bled 295 gm. (approximately 36.7 per cent.) from femoral artery. Blood-pressure fell to 35 and then gradually increased to 50. 10 A. M.: Animal exhibited the signs of shock. Stimulated central end right vagus; blood-pressure increased 40. 10.06 A. M.: Stimulated central end left vagus; blood-pressure increased 45. 10.08 A. M.: Bled from femoral artery, obtaining 200 gm. of blood and 130 gm. from heart. Estimated amount of blood was 810; 61 per cent. was the total amount from artery, 16 per cent. from heart, making 77 per cent., leaving 23 per cent. in the tissues.

The above experiment proves that a free hemorrhage of 36.7 per cent. of an animal's blood, which is the average found to be lost in the shock series, will produce all the clinical signs of shock, and, furthermore, the vasomotor center response to reflex stimulation is identical in shock and in a hemorrhage of this degree. A further comparison of these two experiments shows that shock and hemorrhage have a common cause.

Experiment 19.—March 8, 1915. Dog; male; white mongrel; weight, 13,186 gm.

3.30 P. M.: Etherized. Apparatus arranged to record carotid blood-pressure and to bleed from femoral artery. Right vagus exposed. 3.40 P. M.: Pulse, 220; respiration, 42; blood-pressure, 150. 3.50 P. M.: Sectioned right vagus. 3.55 P. M.: Stimulated central end right vagus; blood-pressure increased 30. 3.56 P. M.: Again stimulated central end of vagus; same result. 3.57 P. M.: Abdomen opened; viscera exposed; blood-pressure gradually fell, but animal did not develop all the signs of shock. 6 P. M.: Animal still requires an anesthetic. Blood-pressure, 85. 6.05 P. M.: Stimulated central end of right vagus; blood-pressure rose 4. 6.06 P. M.: Repeated stimulation; identical result. 6.12

P. M.: Blood-pressure 90. Bled, obtaining 390 gm. of blood from artery and 95 gm. from heart. The estimated amount of blood was 1014 gm.; 38.4 per cent. was secured from the artery and 9.3 from the heart, making a total of 48 per cent., and leaving 52 per cent. in the tissues. This animal had lost physiologically 28 per cent. of its blood, and yet maintained a blood-pressure of 90 and did not develop all the signs of shock (Fig. 229).

Experiment 38.—March 26, 1915. Dog; weight, 8334 gm. 9.45 A. M.: Etherized. Carotid blood-pressure taken. Cannula placed in right femoral artery and left femoral vein. 10.07 A. M.: Blood-pressure 130. 10.10 A. M.: Bled slowly 165 gm. (about 26 per cent.) from femoral vein. Blood-pressure remained at 110. Animal did not show signs of shock. 10.54 A. M.: Blood-pressure, 110; ether still necessary. Bled 64 gm. of blood from vein when cannula blocked by clot. Blood-pressure, 99. The left femoral artery was then opened and 46 gm. (about 7 per cent.) obtained. Bleeding 229 gm. (about 36 per cent.) of blood slowly from the femoral vein decreased blood-pressure 31. Bleeding 46 gm. (about 7 per cent.) from femoral artery decreased blood-pressure 45. 12 A. M.: Animal exhibited signs of shock; bled 140 gm. from artery and 50 gm. from heart. The estimated amount of blood was 642. A total of 65 per cent. was secured from artery and vein, 8 per cent. from the heart, making a total of 73 per cent., leaving 27 per cent. in the tissues (Fig. 230).



Fig. 229 (*Experiment 19*).—Normal blood-pressure, 130. Signals *a* and *b*; *a'* and *b'* mark point of stimulation of central end right vagus. Abdomen opened at *c*. After exposure of viscera blood-pressure fell to 90 and animal did not exhibit all the signs of shock. Note reaction of vasomotor center; 98 per cent. of blood secured from artery and 9 from heart.

Gatch⁶ has shown that the abdominal wall is an important factor in the maintenance of the most efficient mechanism for the return of the blood to the heart. The bearing that this factor

might have on the above method of investigation was tested in these experiments:

Experiment 31.—The animal was given curare until respiratory movements had almost ceased, thus eliminating the effect of abdominal tone before bleeding.

Experiment 37.—The abdomen was widely opened just before bleeding was commenced.

In both these experiments the amount of blood secured was within the normal limits, showing that this factor did not complicate the results.

Other experiments, as section of the splanchnic nerves, transfusion of blood, etc. (Table I and Fig. 231), further emphasized that there is a decrease in blood in shock and that this is not due to a primary failure of the vasomotor mechanism.

SUMMARY OF EXPERIMENTS

The data from the experiments herewith reported may be summarized as follows:

1. In a normal dog 66 per cent. of the blood can be obtained from the femoral artery and 10 per cent. from the heart, making a total of



Fig. 230 (*Experiment 38*).—Normal blood-pressure, 130. Between *a* and *b* 26 per cent. of the blood of the animal was removed by slow hemorrhage from femoral vein. Blood-pressure decreased to 110. Between *c* and *d* 10 per cent. more was removed. Between *d* and *e* bled 7 per cent. from femoral artery. At *f* bled to death from femoral artery.

76 per cent. which can be secured, leaving 24 per cent. in the tissues.

2. In an animal in which the cervical cord is sectioned, producing medullary vasomotor paralysis, 54 per cent. of the blood can be obtained from the femoral artery, and 12 per cent. from the heart, a total of 66 per cent., leaving 34 per cent. in the tissues.

3. In an animal in which blood-pressure is depressed practically to zero by an overdose of ether, 46 per cent. of the blood can be obtained from the femoral artery and 13 per cent. from the heart, making a total of 59 per cent., leaving 41 per cent. in the tissues.

4. In an animal in which the viscera have been exposed until the clinical signs of shock are present, but in which the vasomotor reflexes are as active or even more so than in the normal condition, only 28 per cent. of the blood can be obtained from the femoral artery and 11 per cent. from the heart, making a total of 39 per cent., leaving 61 per cent. in the tissues.

CONCLUSIONS

The clinical signs of shock which appear after section of



Fig. 431 (Experiment 34).—Normal blood-pressure, 100. Right vagus cut at *a*. Central end stimulated at *b* and *c*. Abdomen opened at *d*. Blood-pressure decreased to 30. Animal in deep shock when vagus was again stimulated at *e* and *f*. Note reaction of vasomotor center. At *g* injected 240 gm. of citrated blood (equal to about 35 per cent. of the animal's blood). Blood-pressure at first increased, but in thirty minutes was only 64. Bled at *h*, obtaining 383 gm. from artery and 63 from heart.

the abdomen and exposure of the viscera are due to a loss of circulatory fluid. This loss of fluid is not dependent upon any primary impairment of the medullary vasomotor center, and takes place at a point beyond the control of the vasomotor mechanism. The causes for this loss of fluid are apparently the same as those which determine the accumulation of fluid in any other irritated area, and produce the signs of inflammation. The nervous system probably plays no greater part in the former case than in the latter. The condition is made grave when the viscera are exposed because of the great vascularity of the tissues involved.

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ADDENDA

JOSEPH C. BLOODGOOD

BALTIMORE

In *Progressive Medicine* for December, 1914 (p. 169), I critically reviewed the contribution of Frank C. Mann* on "The Peripheral Origin of Surgical Shock." On December 8, 1914, Dr. Mann wrote me as follows: "Your review of my article contains one criticism which I should like to answer by submitting further data and one misquotation to which, I am sure, your attention only needs to be called to secure its correction."

First, as to the correction: On page 170 of *Progressive Medicine* for December, 1914, I quoted from page 212 of Mann's article, his sixth conclusion. My quotation was as follows: "It is *impossible* to produce signs of shock by the use of excessive heat or cold." The quotation should have read: "It is *possible*, etc."

* Johns Hopkins Hosp. Bull., 1914, xxv, 205.

On page 171 (*ibid.*), in quoting Mann's tenth conclusion, I called attention to the discrepancy in his sixth conclusion. This mistake is mine.

Dr. Mann further writes that on page 172 (*ibid.*) I wrote as follows: "In this paper the details of Mann's experiments are not given, so that it is impossible to study critically the methods of his investigation."

Dr. Mann, in his letter of December 8, tells me that in the original manuscript submitted to the Dean of the Medical Department of the University of Indiana, the experiments were given in detail, but that the editor of the *Johns Hopkins Hospital Bulletin* was of the opinion that it was not necessary to publish them.

This criticism of mine, of course, amounted to very little. It simply meant that from the standpoint of pure physiology one would have been unable to follow Mann's experiments in the laboratory. The omission, however, cannot be blamed on Dr. Mann. Similar experiments are described in detail in Dr. Mann's paper in this issue.

Dr. Mann further writes: "Concerning your other criticisms I must continue to regard them in the light of personal opinion until more data are submitted. I should like to point out, however, that the conclusions of Janeway and Ewing are only slightly different from my own."

This experimental work of Mann was performed under the direction of Dr. W. D. Gatch, Professor of Surgery of the Indiana University.

Dr. Gatch also wrote me about my critical review in *Progressive Medicine*: "I was deeply interested as well as greatly surprised at your review of Dr. Mann's article. I believe that if you had read the article more carefully instead of considering the conclusions entirely apart from the context, you would have agreed with most of the conclusions."

Dr. Gatch writes as follows about Dr. Mann's first conclusion, with which I differed in my critical review: "It is impossible to reduce the anesthetized animal to a state of shock by any degree of sensory stimulation providing all hemorrhage is prevented and its abdomen not opened."

Bloodgood's criticism: "In my experience with operative surgery under general anesthesia in which the condition of the patient has been most carefully recorded and the blood-pressure changes estimated during the entire operation, I have observed extreme degrees of shock in operations other than on the abdomen,

even though there had been no hemorrhage; for example, during operation for old, badly united fractures of the shaft of the femur. In these cases the only factors which could have produced shock were the painful stripping of the periosteum and the extreme extension of the limb."

Dr. Gatch remarks: "In regard to the first conclusion, this is not new; in fact, Porter demonstrated it years ago. Mann demonstrated it beyond a shadow of doubt on 14 dogs. In all of his cases the most extensive traumatization of the extremities was done, all four limbs being amputated and the limbs avulsed with as much roughness as possible. The skin was burned, the skull-cap lifted, and the dura cauterized. All of these manipulations were carried out within a period from four to six hours. The animals' blood-pressure and respirations would show no change from that at the beginning of the experiments,* being in as good condition as at the beginning. Of course, the most scrupulous care was taken to prevent hemorrhage. It is interesting that in two cases in this series in which the signs of shock were developed, we found in one case a large intra-abdominal hemorrhage and in the other an enormous hemorrhage in the legs from fractured bones."

In my criticism, as noted above, of Mann's first conclusion I simply made the statement that my own clinical experience upon the human being could not confirm Mann's first conclusion.

I am not in a position to confirm or controvert Mann's experimental observations. I gather the impression, however, from what Dr. Gatch writes me of Dr. Mann's experience, that this experimental work should rank with the best that has been done in the various experimental and physiologic laboratories. But the very best experimental physiologists have come to different conclusions, and apparently from data gathered from experiments as much alike as it is possible for the different experimenters to make them.

I feel that I must again record my disagreement with Mann's first conclusion based upon the evidence of his experimental work. It may be true for dogs, but it is apparently not true for the human being. I have observed extreme degrees of shock in operations in which the abdomen of the human patient had not been opened and in which there had been no hemorrhage; that is, these patients have shown the same low blood-pressure and the same symptoms which have been called shock when observed in operations upon

* Dr. Mann writes me that all these experiments were done under ether and chloroform anesthesia.

the abdomen. I am also sure that the great majority of surgeons will agree with me.

My criticism, therefore, is not of Mann's experimental work, nor of his conclusions from the evidence of this laboratory investigation. I called attention to this conclusion, because I feared that it might create the impression that trauma in operations other than upon the abdomen was not an important factor in shock.

It is quite true that the same degree of shock experienced in operations on the abdomen is apparently much more serious than when observed in operations without the abdomen. It is also true, from my operative observations, that the prognosis of shock not associated with hemorrhage is as a rule much better than of shock associated with hemorrhage.

Among my records there is an anesthetic chart which portrays an extreme degree of shock apparently due to an overdose of ether only; then a second chart recorded during a shoulder-girdle amputation in which there was practically no hemorrhage. The only etiologic factors for the shock were ether anesthesia and trauma.

The difference of opinion, therefore, between Dr. Mann and myself is that my clinical observations do not confirm his first conclusion.

It is fortunate, however, that Dr. Mann has taken up this physiologic problem, because there have never been enough well-trained workers interested in it.

Dr. Gatch remarks: "In regard to the observation of shock during the operation (upon the human being) there are so many causes by which the signs of shock can be produced, and the term is used so loosely, that I have found it impossible nearly always to say just what was at fault in a given case. My belief is that the depth of narcosis has more to do with it than any other single factor. My reasons for this are set forth at length in a paper* entitled 'The Effect of Laparotomy upon the Circulation,' and also in a paper soon to appear in the *American Journal of Surgery* on 'The Proper Depth of Narcosis.' Mann discusses this point at the beginning of his article, and I am in complete accord with his conclusions that the word *shock* is used almost as vaguely as the word *rheumatism*. The gist of Mann's article is that shock and hemorrhage are practically identical, that experimental shock is simply due to an extensive extravasation of the elements of blood into the peritoneal tissues, that this change is due to a traumatic inflammation, and that the central nervous system has little to do with the

* Trans. Amer. Gynec. Soc., 1914.

condition. Of course, we should use the most extreme care in handling the abdominal viscera. This is not from the danger of nervous stimuli acting upon the central nervous system, but from the danger of traumatic inflammation in the peritoneal cavity."

Mann's conclusion 4: "The vasomotor center is not depressed nor fatigued. It is the most resistant of all vital centers. The peripheral and untraumatized visceral arteries are constricted in shock."

Bloodgood's criticism: "This must be a very difficult thing to prove or disprove. Crile has always favored the theory of fatigue or exhaustion, Meltzer inhibition, while Howell, from his experiments, is of the opinion that there is more than one factor influencing this center. Apparently from the standpoint of pure physiology the exact relationship of the vasomotor center to shock seems still to be theoretical."

There also seems to be a difference of opinion among other contributors.

It is because of this difference of opinion that we can feel quite sure that the problem of the etiologic factors of shock are by no means solved, and for this reason trained experimental surgeons, such as Dr. Mann, are urgently needed and should be welcomed and aided and stimulated by wholesome and honest criticism.

The clinical surgeon whose day's work brings him into intimate contact with the problems of operative mortality and post-operative complications should endeavor to bring before the experimental surgeon his practical needs. Today, in surgery, shock and infection are the most practical problems. The clinical surgeon needs help in both.

In the past, many men have been of the opinion that research work in the various departments of universities has for its object simply the search for the unknown, irrespective of the needs of the community in which the university is situated. In recent years the universities which have apparently made the greatest progress have been those whose research laboratories have worked upon, and solved, problems helpful to the immediate needs of the people; for example, the University of Wisconsin, with its Department of Agriculture, has brought forth the great development of scientific farming in the Northwest.

The laboratories of physiology in many of our universities have not as a rule been interested in solving the problems of the immediate need of the medical profession. Fortunately, in recent years, in some of the medical schools, special departments of experi-

mental surgery and physiology have been organized, often independent of the older departments, and in these new laboratories the workers have been chiefly interested in the investigation of problems of immediate practical importance to the practising surgeon and physician.

In spite of the fact that physiologists have differed as to the exact etiologic factors in shock, their experimental work has been helpful to the surgeon in the recognition, prevention, and treatment of shock.

ELECTIVE LOCALIZATION OF STREPTOCOCCI *

EDWARD C. ROSENOW

The general systemic distribution of microorganisms in certain diseases with a localized focus is well established, but the factors which determine the localization of bacteria after they gain entrance into the circulation are obscure.

In this paper I wish to record a summary of the results obtained from the intravenous injection, under a standard technic, of streptococci isolated from appendicitis, ulcer of the stomach and duodenum, cholecystitis, rheumatic fever, erythema nodosum, herpes zoster, epidemic parotitis, myositis and endocarditis, and to discuss the bearing of these results on localization of streptococci.

TECHNIC

The streptococci were usually grown from sixteen to twenty-four hours at 37° C., in tall columns of ascites (10 per cent.) dextrose (0.2 per cent.) broth (0.6+ to 0.8+) to which sterile tissue (guinea-pig kidney or heart muscle) was often added; the sterility of the ascites fluid and broth containing the tissue was always proved beforehand. After incubation smears were made the cultures were centrifuged in the containers in which they were cultivated,† the supernatant fluid was decanted, and the sediment suspended in sodium chlorid solution so that 1 c.c. of the suspension contained

* From the Memorial Institute of Infectious Diseases, Chicago, and the Mayo Foundation, Rochester, Minn. Reprinted from Jour. Amer. Med. Assoc., 1915, lxx, 1687-1691.

† The common eight-ounce nursing bottle is used both as a culture flask and centrifugal tube, and serves the purpose admirably.

the growth from 15 c.c. of broth. The doses for rabbits (ear vein) were usually from 0.5 to 3 c.c., and for dogs (leg vein) from 1 to 5 c.c. of this suspension. The injections were made quite rapidly through a rather fine needle (22 gage), usually within an hour after the suspension was made. Blood-agar plate cultures were made at the time the suspensions were injected to study the character of the organisms, to test their viability, and to save them for further study. This is an important precaution because negative results have at times proved to be due to early death of the recently isolated organisms in the broth cultures. In the accompanying table, "when isolated" indicates the first or second and, occasionally, the third or fourth cultures, or the first culture after one animal passage. "Later" indicates that the strains were cultivated for a week or longer. "After animal passage" indicates usually from the second to the sixth animal passage.

The strains tested from appendicitis, ulcer of the stomach, cholecystitis, rheumatic fever, erythema nodosum, myositis, and endocarditis include strains isolated from the characteristic lesions as well as from the apparent atrium of infection. Those from herpes zoster were from the tonsils and spinal fluid, and those from epidemic parotitis were obtained by catheterizing Steno's duct and from the tonsils. The strains from miscellaneous sources were usually from tonsils approaching the normal condition; and the laboratory strains were streptococci or pneumococci cultivated on artificial mediums for a long time and had lost all apparent virulence. The figures in the lowest line of the table represent the average percentage incidence of lesions in individual organs following injection of various strains of streptococci except those from the specific disease. Thus the first figure indicates that 5 per cent. of the animals injected with the various strains, except those from appendicitis, showed lesions in the appendix.

Care was exercised to obtain growths from the depths of the supposed primary focus with as little contamination from the surface as possible, the cultures being made from the material expressed from the tonsils or from emulsion of extirpated tonsils after thorough washing in sodium chlorid solution. The material

from the depths of pyorrheal pockets was obtained by means of a pipet.

For the study of pathogenicity of the cultures, dogs and rabbits were chiefly used, being killed with chloroform at the desired time, usually in from twenty-four to forty-eight hours. Post-mortem examinations were always made as soon after death as possible. A thorough inspection in a bright light with the unaided eye or with the aid of a hand lens was made for focal lesions. The exact character of the lesions and the presence of the streptococci in each of the various diseases have been determined by microscopic study of sections. Cloudy swelling is not included in the results given in the table. Hemorrhage, localized necrosis, exudation, and infiltration were the usual lesions. Thus, in case of the joints, hemorrhage about the joint or turbidity of fluid, as determined with a pipet, or both, were considered as evidence of arthritis. Hemorrhages in the pericardium and turbidity of pericardial fluid, due to leukocytes, were considered as evidence of pericarditis. The postmortem study of animals often symptomless is essential to obtain accurate knowledge of the pathogenicity of a culture, and must supplant the older method of merely finding out whether or not a culture produces death, a method still too much in vogue. The table includes data only from those animals in which the postmortem was comprehensive, and does not include some of the earlier experiments, especially on endocarditis. Increase in mortality rate, earlier death, and greater degree and distribution of lesions following standard dosage were considered as proof of high virulence. Changes in the spleen and liver were so rare following injection of the strains as isolated, except those from cholecystitis, that they are not included in the table. Acute splenitis and such changes in the liver as focal necrosis, parenchymatous and bile-duct hemorrhages, and acute degeneration with marked acidity occurred, however, after the strains had acquired greater virulence from animal passage. In the earlier experiments not sufficient attention was paid to the occurrence of lesions in the thyroid, thymus, suprarenals, and lymphatic glands. Later a closer search for lesions in these structures was made, especially

after it was found that lesions in the thyroid followed intravenous injection of bacteria isolated from goiter. It must be said, too, that strains of streptococci from rheumatic fever, myositis, and cholecystitis produce hemorrhages in the thyroid quite commonly, while those from other sources rarely produce them.

RESULTS

A study of the table shows that streptococci from the various diseases often have a most striking affinity or tropism for the organs or tissues from which they are isolated. Thus, 14 strains from appendicitis produced lesions in the appendix in 68 per cent. of the 68 rabbits injected, which is in marked contrast to an average of only 5 per cent. (given in lowest line of table) of lesions in the appendix in the animals injected with the strains as isolated from sources other than appendicitis. Eighteen strains from ulcer of the stomach or duodenum produced hemorrhages in 60 per cent. and ulcer of the stomach or duodenum in 60 per cent., a combined total of 74 per cent. of the 103 animals injected, in contrast to an average of 20 per cent. hemorrhages and 9 per cent. ulcer following injection of other strains. Twelve strains from cholecystitis produced lesions in the gall-bladder in 80 per cent. of the 41 animals injected, in contrast to an average incidence of lesions here of only 11 per cent. with the other strains. Twenty-four strains from rheumatic fever produced arthritis in 66 per cent., endocarditis in 46 per cent., pericarditis in 27 per cent., and myocarditis in 44 per cent. of the 71 animals injected, in contrast to an average of arthritis in 27 per cent., endocardial lesions in 14 per cent., pericarditis in 2 per cent., and myocarditis in 10 per cent. of the animals injected with strains from sources other than rheumatic fever. Six strains from erythema nodosum produced lesions of the skin in 90 per cent. of 20 animals injected, in contrast to an average of 2 per cent. in the animals injected with the strains from sources other than erythema nodosum and herpes zoster. Eleven strains from herpes zoster produced herpetiform lesions of the skin, lips, tongue, or conjunctivæ in 77 per cent. of the 61 animals injected, in contrast to the average of only 1 per cent. of what

seemed to be herpes of the skin with the other strains. Nine strains of streptococcal organism from epidemic parotitis produced lesions in one or both parotid glands in 73 per cent. of the 19 animals injected intravenously, in contrast to no instance of lesions here with the other strains. Three strains from cases of true myositis produced myositis in 75 per cent. and myocarditis (chiefly of the right ventricle) in 35 per cent. of the 40 animals injected, in contrast to an average of myositis of 12 per cent. and myocarditis of 10 per cent. following injection of strains from sources other than myositis or rheumatic fever; and eight strains of *Streptococcus viridans* from chronic septic endocarditis produced lesions in the endocardium in 84 per cent. of the 44 animals injected, in contrast to an average of 15 per cent. with the strains other than those from endocarditis. The results following injection of the miscellaneous strains (usually the first culture from tonsils) and the laboratory strains serve as a basis of comparison with those following injection of the strains from the various diseases, and correspond roughly with the total average incidence of lesions in the various organs as given in the lowest line of the table.

While the incidence of lesions in the organs following injection of the strains isolated from such organs is high, as shown by these figures, the appearances at the necropsy are even more significant. In many instances in which the animals survive the injection for some time, no other focal lesions could be found except those in the organ in question; and when the animal died early, these lesions were the marked feature and the associated ones were relatively insignificant. Frequently the injection of a very small dose was sufficient to prove the elective localization. This elective property was shown not only by the cultures from tissues and foci, but also by the bacteria contained in the foci, directly injected in other animals.

In many cases of both acute and chronic diseases the apparent atrium of infection was found to harbor streptococci having elective affinity; in the former usually only at the time of the attack, in the latter in some instances for months. The elective affinity, however, was less marked in the strains isolated from the supposed

focus than in the strains isolated from the lesions in the various organs. The rather wide range of lesions, as indicated in the table, following the injection of the strains from herpes zoster and parotitis, is due to the fact that often primary mixed cultures from tonsils and pyorrheal pockets were injected.

Attempts to find a method which would preserve the original tropic property, while only partially successful, have shown that it may be preserved for some weeks in the deeper colonies of the original shake cultures and for as long as seven months by keeping the suspensions containing sterile tissue in the ice-chest, thus maintaining the bacteria in a condition of latent life.

The localization of the strains from appendicitis, ulcer of the stomach, and cholecystitis as isolated, after cultivation and after animal passage, is of particular interest, and will be discussed in a separate paper. It should be stated here, however, that these strains resemble one another very closely indeed in cultural and other respects. Those from appendicitis are the least virulent, those from ulcer occupy a middle position, and those from cholecystitis are the most virulent. The virulence seems to be one of the factors that determines their place of survival after intravenous injection. Now if the localization is dependent to a certain extent on virulence, then the occurrence of ulcer and cholecystitis should become greater as the strains from the appendix are passed through animals, and appendicitis should occur oftener after the strains from ulcer and cholecystitis lose virulence from cultivation on artificial mediums. This is found actually to be the case (see figures in table). In this connection other facts should be mentioned. None of the strains from appendicitis produced pancreatitis. The strains from ulcer and cholecystitis as isolated (mostly those from acute cases) produced pancreatitis in 3 per cent. and 5 per cent., respectively, of the animals injected. After animal passage, pancreatitis occurred in 15 and 19 per cent., respectively, while after cultivation on artificial mediums pancreatitis was not obtained.

Lesions in the intestines, exclusive of the duodenum, were more common with the strains from cholecystitis and rheumatism than

SOURCE OF STREPTOCOCCI		STRAINS (220)	ANIMALS INJECTED (229)	PERCENTAGE OF ANIMALS SHOWING LESIONS IN															
				Stomach		Gall-bladder	Pancreas	Intestines	Joints	Endocardium	Pericardium	Myocardium	Muscles	Kidney	Lung	Skin	Tongue	Eye	Parotid
				Hem- or- rha- ge	Ulcer														
Appendicitis	When isolated.....	14	68	6	1	0	0	9	29	21	0	9	12	0	0	0	0	0	0
	Later.....	8	26	15	15	4	0	0	22	19	0	12	23	0	0	0	0	0	0
	After animal passage.....	7	45	30	40	0	0	20	36	20	0	20	25	10	0	0	0	0	0
Ulcer of stomach in man	When isolated.....	18	103	60	60	20	5	7	16	12	4	5	0	5	0	0	0	0	0
	Later.....	8	42	5	0	0	0	0	18	14	0	0	0	0	0	0	0	0	0
	After animal passage.....	7	39	0	25	33	50	15	91	5	0	3	8	15	0	0	0	0	0
Cholecystitis	When isolated.....	12	41	0	29	15	80	5	17	10	0	2	7	5	2	0	0	0	0
	Later.....	5	14	28	14	7	0	0	21	14	0	0	0	7	0	0	0	0	0
	After animal passage.....	4	16	0	31	56	19	13	25	19	0	15	6	0	0	0	0	0	0
Rheumatic fever	When isolated.....	24	71	8	23	18	3	13	66	46	27	44	27	39	4	6	0	10	0
	Later.....	8	14	0	14	21	0	0	21	21	0	28	0	21	0	0	0	0	0
	After animal passage.....	5	19	21	37	21	5	21	57	53	32	37	16	42	21	0	0	11	0
Erythema nodosum	When isolated.....	6	20	0	10	0	0	5	20	10	0	35	10	5	90	0	5	0	0
	Later.....	3	9	0	22	0	11	0	11	11	0	0	0	0	0	92	0	0	0
	After animal passage.....	6	14	0	21	0	50	0	50	14	7	14	50	7	43	43	0	0	0
Herpes zoster	When isolated.....	11	61	10	39	8	16	2	8	11	5	11	5	5	21	70	15	15	0
	Later.....	6	15	0	15	7	7	13	7	60	7	40	40	7	20	7	0	13	0
	After animal passage.....	4	7	0	28	10	0	0	0	43	0	14	0	28	0	43	28	14	0
Mumps	When isolated.....	9	19	15	21	5	21	42	10	42	15	0	37	3	5	15	15	0	0
	Later.....	5	8	12	0	0	12	12	24	24	0	12	12	0	12	12	0	0	24
	When isolated.....	3	40	2	4	10	2	7	20	10	0	35	75	2	0	7	0	8	0
Myositis	When isolated.....	8	44	0	7	0	5	0	15	15	4	20	0	20	20	2	0	0	0
	Later.....	34	41	3	17	0	4	0	17	20	0	15	7	7	7	0	0	0	0
	After animal passage.....	5	100	2	18	5	2	2	45	49	0	15	12	10	17	2	0	6	0
Average percentage of animals injected with non-specific strains showing lesions in individual organs.....				5	20	9	11												

with those from appendicitis, and all the strains produced intestinal lesions (chiefly of the mucous membrane and lymphoid structures) quite commonly after they had been passed through animals, whereas after cultivation for a time no noteworthy lesions were found in the intestinal tract.

The streptococci studied by me from parotitis resemble the organism described by Herb¹ and, like hers, produced the characteristic picture of mumps in dogs when injected into Steno's duct. Intravenous injection of these organisms produced marked edema and hemorrhage in and surrounding the parotid. The affinity was so great that the streptococci were found in pure culture in the enlarged parotid in three of five full-time puppies removed from the uterus of a dog which was chloroformed during a marked parotitis following injection into Steno's duct. Antigens prepared from a number of these strains were found to bind specifically complement in serum from parotitis (Howell).

Lesions in the skeletal muscles occurred in 75 per cent. of the animals injected. The number of lesions in the muscles and myocardium in the animals injected with strains from myositis was often in proportion to the quantity injected, and occurred mostly in the tendinous portion and in the right ventricle.

Lesions in the kidney were especially common after injections of streptococci from rheumatic fever (39 per cent.) and from endocarditis (20 per cent.). These occurred chiefly in the medullary portion (Rosenow³) in the former and in the glomeruli in the latter.

Lesions in the lung, consisting usually of hemorrhages and edema, were rare following injection of the strains when isolated and after they were cultivated on artificial mediums but, just as was found previously (Rosenow²), they occurred oftener after the virulence was increased by animal passage.

That the streptococci are the underlying cause of the diseases from the lesions of which they were isolated is indicated further by the fact that they have elective affinity for the corresponding structures in animals. Moreover, the fact that the same streptococcus may be made to localize in different organs is in consonance with the knowledge that streptococci may cause diseases with

different symptomatology. The possibility, however, that they are secondary invaders to some ultramicroscopic, filterable organism has to be considered. Filtrates of the streptococcal cultures from various diseases were injected intravenously. In some instances the filtrates produced lesions in the organs from which the strains were isolated; the lesions, however, were not due to living organisms, because the broth which was inoculated and incubated with the tissues failed to produce any lesions. The results, while inconclusive, may be said to indicate that streptococci produce substances which cause injury specifically in the tissues from which the strains are isolated.

GENERAL DISCUSSION

The results obtained are in harmony with the facts that—(1) “septic sore throat” is due to streptococci having peculiar properties³; (2) certain epidemics of throat infection, due to streptococci, are more frequently complicated by sinusitis than others; (3) distinct differences in the character of the lesion in the lung and mortality rate in pneumonia, as shown by Cole,⁴ are due to pneumococci so nearly alike as to require sensitive biologic tests to differentiate them; (4) hemolytic streptococci frequently have a marked affinity for joints, and (5) Friedländer bacilli in arthritis show elective affinity for joints in animals when other strains do not (Dick⁵). The “organotropic” condition of streptococci is analogous to the affinity of the tetanus toxin for the motor ganglion cells, of the diphtheria bacillus for the faucial tonsils, of the meningococcus for the meninges, of the pneumococcus for the lung, of the typhoid bacillus for lymphatic tissues, of the virus of rabies for the central nervous system, of the organism of anterior poliomyelitis for the anterior horns of the spinal cord, of the malarial parasite for the red blood-corpuscle, and of the *Trichina spiralis* for muscles. The results, moreover, are in accord with the well-known fact that chemicals when injected intravenously also localize unequally in various organs.⁶ The changes in the distribution of lesions as the streptococci are altered by cultivation on artificial mediums or by animal passage are similar to the changes in

localization of various chemicals or dyes depending on chemical constitution, as observed by Ehrlich.⁷ In my experiments advantage was taken of the opportunity afforded to study the nature of selective action from the standpoint of living bacteria.

Flexner⁸ has shown that the functioning organ may be especially favorable to the growth of certain bacteria, although the organ extracts may inhibit their growth; hence the growth of bacteria in various organs may be related to function and blood supply. Streptococci of low virulence but highly sensitive to oxygen are found to produce lesions in tissues whose blood supply and therefore oxygen and food requirements are low (heart-valves, tendinous portion of muscles, and the structures about joints). Streptococci of greater virulence are found to produce lesions in tissues whose blood supply and therefore oxygen and food requirements are high (kidney, lung, etc.); hence localization and production of injury seem to be closely related to the amount of available oxygen in a given tissue. The fact that lesions occurred far more frequently in the right ventricle (containing venous blood) than in the left ventricle (containing oxygenated blood) is in accord with this hypothesis. Might not the predisposing action of trauma (*locus minoris resistentiæ*), of exposure to cold, and of a drunken bout, to infection be best explained on the basis of lack of oxygen?

The changes observed, as hemorrhage, cloudy swelling, and necrosis, from a purely chemical⁹ as well as from a colloid-chemical¹⁰ point of view, are identical with the changes of tissue asphyxia. I have found that pneumococci when grown and autolyzed under anaërobic conditions produce a much larger quantity of toxic material than when grown or autolyzed under aërobic conditions. Moreover, pneumococcus extracts proved to be toxic to warm-blooded animals (guinea-pigs) have the same inhibitory effect on the development of fertilized eggs of *Arbacia* as does lack of oxygen. Since bacteria and their products are powerful reducing agents,¹¹ one of the chief effects of the bacteria and their products very likely is interference with the normal cell respiration, and possibly the greater the virulence, the more powerful this interference.

Although the circulation is an important factor in determining localization, the tissues themselves play an even more important rôle. The question whether the lesions in the organ for which a particular strain appears to have elective affinity are due to the lodgment of a larger number of bacteria here than in the other organs, or whether the bacteria lodge in equal numbers in the various organs but survive only in the one showing lesions, is now under study. The evidence already obtained, however, points strongly to the former mechanism. It appears that the cells of the tissues for which a given strain shows elective affinity take the bacteria out of the circulation as if by a magnet—adsorption.

This remarkable tropic condition tends to disappear quite promptly, both on cultivating the streptococci on artificial mediums and on passing them successively through animals, and this may occur without demonstrable changes in morphology, grouping, or character of chain formation. I have previously shown¹² that the ability of *Streptococcus viridans* and staphylococci to produce lesions in the endocardium is due partly to physical clumping. Evans¹³ has shown that the action of vital stains of the benzidin group is related to the size of colloidal particles. A careful study of smears of the suspensions injected in these experiments revealed no constant relation between localization and clumping or size of the bacteria.

Individual variations in resistance to infection were found in the injected animals. The effects of these conditions in the host as determining factors in localization are important; they are probably expressions of differences in metabolism, oxidation rates, etc., which influence the soil for bacteria. The tendency of virulent bacteria, temporarily or permanently, to render this soil less favorable for their growth is well established. There is some evidence, on the other hand, which goes to show that certain bacteria of very low virulence (commonly found in chronic foci of infection) tend actually to make this soil more favorable. But, in the light of my results, it must be considered that differences in the host may afford the peculiar type of reaction, or that the individual harbors a particular form of focus of infection which is favorable for

bacteria to acquire elective properties. The following facts support the latter view: (1) The common occurrence of certain non-contagious diseases, such as herpes zoster, ulcer of the stomach, etc., during definite age periods; (2) the fact that foci of infection afford opportunity for bacteria to grow under varying grades of oxygen pressure and in mixed culture, both of which have been shown to cause changes in virulence and other properties of bacteria,¹⁴ including the streptococcus group;¹⁵ (3) the occurrence of systemic infections, such as rheumatic fever, appendicitis, ulcer of the stomach, etc., usually after the acute symptoms in follicular tonsillitis (hemolytic streptococci) have subsided, and (4) the finding, in the focus and involved tissues at the time of the systemic infection, of streptococci having elective affinity for these structures in animals.

Since different bacteria may acquire simultaneously affinity for the same tissue, diseases which resemble each other more or less closely, such as the different forms of arthritis, may be due to bacteria of different species, each having elective affinity for the particular structures involved.

The figures in the lowest line of the table represent the results of numerous experiments (833) with streptococci (220) from a wide range of sources, and may therefore be regarded as an index of the liability of the various organs to infection. Thus, joint lesions occurred more often (27 per cent.) than lesions in other organs, corresponding to the frequent occurrence of spontaneous arthritis in man and animals. The occurrence of lesions in the stomach (20 per cent.), valves of the heart (14 per cent.), myocardium (12 per cent.), and skeletal muscles (12 per cent.) correspond in a general way to the occurrence of infection in these organs in man. The very infrequent involvement of the skin, tongue, and the parotid in the animals is in keeping with the rarity of embolic infections in these structures. The character of the lesions and their occurrence simultaneously in the joints, heart, muscles, and kidney, and the development of chorea (7 per cent., mostly in young rabbits) following injection of the streptococci from rheumatic fever, parallels quite closely the phenomena of rheumatic infection as observed in

man. The strains from erythema nodosum resemble those from rheumatic fever, producing a relatively high incidence of arthritis, pericarditis, and myositis, a fact which supports the view held by clinical observers,¹⁶ that the causative agents of rheumatic fever and erythema nodosum must be similar.

The tendency to localize electively within a limited range, "monotropism," is most highly developed in the relatively non-virulent strains isolated from chronic lesions. In the more virulent strains from acute lesions and after animal passage, this tendency is less highly developed, the lesions occurring over a wider range, "polytropism." The fact that the elective property is more highly developed in streptococci isolated from the organ involved, than in those isolated from the probable focus of infection, is in accord with the results obtained by Forssner,¹⁷ who showed that when streptococci are grown in kidney and kidney extracts they acquire a special predilection for the kidney when injected intravenously. Since the bacteria which have grown in a given tissue acquire greater affinity for this tissue, the likelihood of these bacteria to involve other structures is relatively slight; hence the secondary focus, a cholecystitis, for example, would appear to be less important as a distributor of bacteria than the primary focus; if, however, the secondary focus happens to be in a joint, of which there are many, it may play an important rôle in causing extension to uninvolved joints and in preventing recovery.

The bearing that these results have on the specific treatment of these diseases is evident. The injection of a streptococcus vaccine or antistreptococcus serum without regard to the tropic condition of the infecting strain or the one used in their preparation is, in the light of these results, far from an exact method of treatment. However, the occasional, seemingly good result observed by some may be due to the use of a serum or vaccine made from strains in the same tropic condition as the one infecting the individual so treated.

The results detailed in this and in previous papers seem to bring the necessary experimental proof that chronic foci of infection play a most important rôle in causing systemic disease, a fact which has

been observed and frequently commented on by different observers, but has been recognized in its full clinical significance especially by Billings.¹⁸ A focus, such as a pocket in the tonsil which cannot heal for mechanical reasons, and which is constantly filled with pus and necrotic material, teeming with bacteria, must be regarded in the light of these findings as a culture tube with a permeable wall affording abundant opportunity for the entrance of bacteria and their products.

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THE ETIOLOGY AND EXPERIMENTAL PRODUCTION OF HERPES ZOSTER

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In our preliminary note ¹ we reported the production of herpes of the skin, tongue, and lips, and lesions in the corresponding ganglia, in a large number of animals injected with streptococci isolated from the tonsils, the pyorrheal pockets, the sputum, and spinal fluid in herpes in man. In this paper we wish to review briefly the development of our knowledge of herpes, record the results of the cultures and other findings in the cases studied, give details of representative experiments, and discuss the significance of our results.

HISTORIC REVIEW

The first reliable report of observations concerning the etiology of herpes zoster was that of von Bärensprung² in 1861. He advanced the theory of a nervous origin, and later³ demonstrated an acute inflammatory condition of the ganglion corresponding to the region affected. C. Boeck, in 1878, demonstrated pus infiltration of the Gasserian ganglion in the case of a girl who died with meningeal symptoms, and in whom herpes of the face had developed. Wyss⁴ and Sattler⁵ each reported a case of zoster of the ophthalmic branch of the trigeminal nerve. In the former of these, in which death occurred seven days after the appearance of the eruption, hemorrhages were noted in and around the Gasserian ganglion; there was interstitial "purulent inflammation" of the ganglion and small abscesses of the eye muscles. In the latter, with death fourteen days after the eruption, there were found

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round-cell infiltration of the ganglion, destruction of the ganglion-cells, and degeneration of the ophthalmic nerve, the other two branches of the trigeminal nerve being normal. Lesser⁶ reported three cases of zoster of the trunk in which degenerative changes and hemorrhages were found within and surrounding the ganglia corresponding to the area of herpes. In 1900 the classic work of Head and Campbell⁷ appeared in which the etiology of herpes zoster was thoroughly considered on the basis of pathologic findings in 15 autopsies and 400 clinical cases which came under Head's⁸ observation during his notable work on the subject of referred pain in visceral disease. They conclude that herpes zoster is a specific infectious disease which confers immunity, the number of recurrences being between 1 and 2 per cent.; that the specific virus has an affinity for the nervous system, particularly for the ganglia, in which there are found inflammatory changes, acute or chronic, according to the length of time between the appearance of the eruption and death. They propose to consider the disease as an acute posterior poliomyelitis, in contradistinction to acute anterior poliomyelitis. They were unable to demonstrate microorganisms in the affected ganglia. There is much other evidence tending to prove the infectious nature of the disease. As early as 1892 Head described a form of herpes as an acute specific infection. Blaschko⁹ corroborated many of the findings of Head and Campbell, and described several cases of herpes zoster with febrile disturbances and swelling of the regional lymphatic glands. Oppenheim¹⁰ cited the case of a young man with a bilateral zoster in the ulnar region which was accompanied by severe swelling of the glands. He also stated that epidemics of the disease have been reported, notably, as cited by Oppenheim, by Rohi, Kaposi, Weis, Reily, and Dopter, in the latter instance a house epidemic. Sachs¹¹ reported an epidemic that occurred in Breslau.

Microorganisms (diplococci) have been demonstrated in the spinal fluid by Achard and Leoper, Widal, Brissaud-Siccard (Oppenheim). Magnus¹² reported a case which is very interesting, in view of our experimental observations. The patient, a man forty-one years of age, had an attack of rheumatism six years before the

last illness; otherwise he had been well. His last illness was marked by grave motor disturbances, and three weeks before death there developed a herpes zoster over the left side of the chest. Of the 20 spinal ganglia examined, pathologic changes were found only in the third dorsal; hemorrhages were visible macroscopically, while microscopically there was an engorgement of the blood-vessels, and these were surrounded by marked areas of round-cell infiltration which were continued into the periphery of the ganglion. In the ganglion proper there were hemorrhages and areas where only remnants of the ganglion-cells remained. The round-cell infiltration was especially marked in the periphery, about the blood-vessels. It was not diffuse, but occurred in small circumscribed areas. A painstaking search failed to reveal any microorganisms in the ganglia. The findings in the cord were significant. In the second and eighth cervical, the first, second, third, fifth, and sixth dorsal segments, there were found circumscribed areas of round-cell infiltration, especially marked about the arteria centralis and its anterior horn ramifications. In the second dorsal segment in the center of the anterior horn, within an area of round-cell infiltration adjacent to an engorged blood-vessel, diplococci were demonstrated.

Finally, Sunde¹³ reported a case of ophthalmic herpes in which he found diplococci in the hemorrhagic Gasserian ganglion.

Howard¹⁴ has shown that the character of the reaction in the skin in simple herpes does not differ essentially from those in zoster, and that simple herpes of the skin about the nose and lips, just as herpes of the trunk in pneumonia and meningitis, is associated with lesions of the Gasserian and spinal ganglia.

Trevisanello¹⁵ isolated pneumococci from the vesicles in herpes of the lips in four cases of pneumonia, and reproduced vesicular lesions by inoculating the organism in normal areas of skin in the same individual. The virulence of pneumococci was low, but could be increased with successive animal passages (white mice). Since pneumococci were recovered from the blood also, there is no reason to doubt the occurrence of lesions in the ganglia in these cases.

That herpes occurs in the mucous membranes of the viscera, the respiratory and digestive system, and the kidneys has been the belief of some close clinical observers. Fernet¹⁶ cites several cases in which the relation between visceral disturbances and a concomitant herpes zoster was very striking, this being particularly true of a certain type of pharyngitis ("angine herpetique") and fibrinous pneumonia. Fernet believes that the former is due to an inflammation of the glossopharyngeal nerve, and the latter to lesions along the vagus and sympathetic, affecting the peripheral nerve-endings, which ramify in one or more of the lobes of the lungs. He calls attention to the fact that herpes labialis, so commonly found in these diseases, occurs invariably on the same side as the pneumonia or angina. As evidence of herpes occurring in the digestive tract, he cites, among other cases, the following: A five-year-old boy was seized in the evening with high fever, accompanied by severe chills which continued throughout the night. In the morning the temperature was lower, but a marked angina was present, which subsided the following day. Two days later there was a similar attack of fever, this time followed by a marked herpes of the face, neck, trunk, and extremities. The second day of this attack the patient had colic, with a profuse discharge of mucus and slightly blood-tinged stools. These attacks lasted three days and the symptoms disappeared together with those of herpes of the skin. The evidence seems strongly in favor of a herpes of the lower bowel.

Bittorf,¹⁷ Kanëra,¹⁸ Rosenberg,¹⁹ and Rosenbaum²⁰ reported cases of renal colic appearing simultaneously with herpes zoster corresponding to the affected kidney. Vetleson²¹ cited a case in which there was apparently a herpes of the lower intestinal tract, the patient, on the second day after the eruption of an inguino-femoral zoster, complaining of a similar pain associated with colic in the lower abdomen. In this case cultures were made, and from the herpetic vesicles and spinal fluid a Gram-positive non-encapsulated diplococcus was isolated. Vetleson cited another interesting case in which pneumonia, meningitis, appendicitis, and herpes facialis occurred concomitantly. He considers this an

illustration of a spread of the infection along the nerve-trunks upward through the cervical ganglion to the meninges, and downward, along the vagus and sympathetic, to the lungs and appendix.

Hunt²² suggested that the attacks of vomiting and slow, irregular pulse in a case of herpes of the ear were probably due to involvement of the vagus. However, postmortem records in which lesions of the visceral nerves or ganglia have been demonstrated cannot be found. The finding of diplococci in the blister fluid, the spinal fluid, and in the ganglia in the above isolated instances suggests strongly that herpes zoster is a streptococcus infection. The necessary experimental proof, however, has heretofore not been brought forward.

TECHNIC

The technic employed in the experimental production of herpes zoster was essentially that used by one of us (Rosenow²³) in connection with experiments on appendicitis, erythema nodosum, and ulcer of the stomach. The cultures were made by expressing pus from crypts and abscesses in the tonsils, from the depths of pyorrheal pockets, and from blister-fluid obtained by means of sterile pipets. The spinal fluid was obtained by aspirating it gently into a sterile glass syringe so as to avoid possible contamination from the air. Inoculations were made on blood-agar plates and blood-agar slants (the former incubated aërobically, the latter anaërobically), and into tall columns (10 to 12 cm.) of 0.2 per cent. dextrose broth, to which sterile ascites fluid and sterile tissue were usually added. The cultures for injection were incubated from eighteen to forty-eight hours at 37° C., the bacteria sedimented in the containers in which they were cultivated, the supernatant clear fluid decanted, and suspensions made in salt solution so that 1 c.c. of the emulsion contained the growth from 15 c.c. of broth. In all instances at the time of injection control cultures were made of the suspensions on blood-agar plates to prove the viability of the organisms and to study them further. The injections were usually made intravenously, but intraperitoneal and subcutaneous injections were made in some instances, and included emulsions

of extirpated tonsils, mixed cultures obtained from tonsils and pyorrheal pockets, pure cultures of streptococci from the spinal fluid in herpes zoster in man, and pure cultures of streptococci obtained from the spinal fluid or ganglia in animals showing experimental herpes. The primary cultures from the foci, usually mixtures of streptococci and staphylococci, were often injected directly and the bacteria studied later. The animals were handled carefully, examined daily, and often caged separately so as to avoid accidental lesions of the skin which might be mistaken for herpes. Herpes about the mouth, tongue, or eyes was easily detected, while, owing to the large amount of hair, herpes of the trunk was found during life only when the lesions were marked. The lesions of the trunk were best observed on the under surface of the skin after death. Chloroform was used to kill the animals that survived the injection (60 per cent.). The examinations were made as soon after death as possible.

In order to be sure that the streptococcus in herpes was not merely an invader of the ganglia secondary to some unknown filterable virus, injections were made of the filtrates of the streptococcus cultures. Tissues for microscopic study were fixed in formalin and Zenker's fluid. The sections were stained with hematoxylin and eosin and for bacteria by the Gram-Weigert method.

REVIEW OF CASES; RESULTS OF CULTURES AND ANIMAL EXPERIMENTS

The following is a review of the clinical facts in the cases studied, the results of the cultures and animal experiments and the details of representative experiment in each.

CASE 267.—Recurring brachial herpes in a woman forty-five years of age, otherwise in good health. The attacks had occurred usually in the spring and fall, following contraction of a cold, but without symptoms of distinct tonsillitis. *February 10, 1915*, the tonsils were examined and found small, atrophic, and covered by the anterior pillars. Cultures were made from the pus expressed from pockets in the tonsils, and on *February 13th* practically

pure cultures of streptococcus, green-producing on blood agar, short chained in ascites-dextrose broth, were demonstrated.

Four guinea-pigs, three rabbits, and one dog were injected; all showed herpes of the skin or mucous membrane of the tongue.

Rabbit 33, injected February 11, 1915, with the growth from 30 c.c. of ascites-dextrose-tissue broth, was found dead *February 12th*. On removing the skin several hemorrhagic vesicular areas

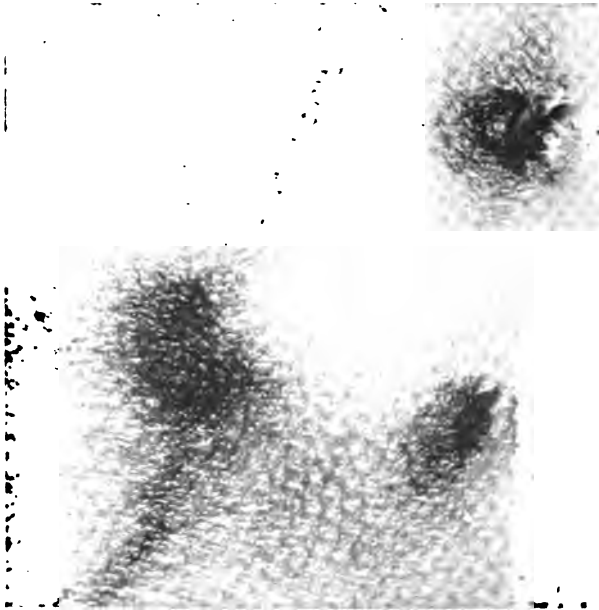


Fig. 232.—Herpes as seen on the under surface of the skin, over the lower right thoracic region, in a rabbit twenty-four hours after an intravenous injection of the streptococcus from herpes zoster (281). Note particularly the vesicular character of one of the lesions (natural size).

were found over the left shoulder. A number of hemorrhagic vesicles were found at the juncture of the mucous membrane of the upper lip and skin, and adjacent to the lower incisor teeth. The tongue showed numerous vesicular areas, many of which were ruptured, and, as a result, much of the mucous membrane of the tongue was absent (Fig. 247). The Gasserian ganglia appeared edematous, and on cross-section showed small hemorrhagic areas. The third and fourth left dorsal ganglia, corresponding to the area of herpes over the shoulder, were hemorrhagic, and there were a

few small hemorrhages in the peritoneal coat of the appendix and sigmoid, two rather large, edematous, hemorrhagic areas of the mucous membrane of the stomach, and marked degeneration and acidity of the liver. There were no hemorrhages of the meninges, brain, or cord. The spinal fluid was slightly turbid and tinged with blood. On *February 13th* blood-agar plate cultures made from the blood and from the fluid aspirated from the hemorrhages in the skin showed a large number of streptococci and a moderate number of staphylococci. Sections of the upper lip through the herpes



Fig. 233.—Herpes of the skin of the upper aspect of the right thigh of Rabbit 62, forty-eight hours after an intravenous injection of the streptococcus from the tonsil in Case 281 ($\times 4$).

area showed desquamation of epithelium and separation of cells, together with infiltration of the epidermis with red blood-corpuscles and a few round-cells (Fig. 248, *a*). In the deeper layers of the hemorrhagic area (Fig. 248, *b*) were a thrombosed blood-vessel (Fig. 248, *c*) and a rather large number of diplococci and chains, while near the surface staphylococci also were found. No bacteria were found in blood-vessels that did not show changes, but in the thrombosed vessels a moderate number of streptococci were disclosed (Fig. 249). Also portions of the sections that did not show changes were free from bacteria.

CASE 270.—Typical acute thoracic herpes zoster in a woman forty-five years of age. Without known cause the attack began *February 9th* with severe pain in right side of chest. The patient once had frequent attacks of tonsillitis, but none since she had had acute rheumatic fever associated with jaundice thirteen years before. For the past three months she had lost in weight and had

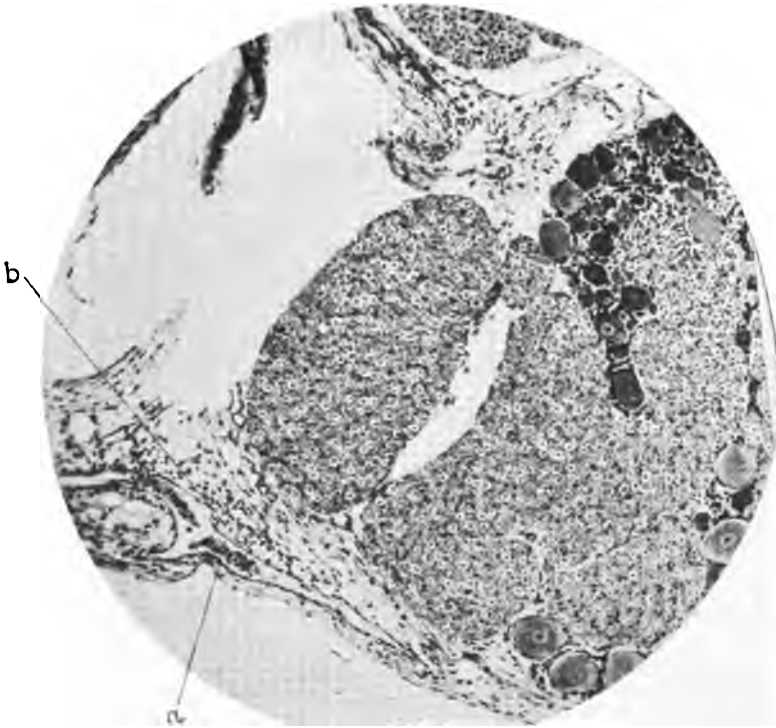


Fig. 234.—Thrombosis of the vein (a) and perivascular infiltration (b) of the posterior root adjacent to the ganglion corresponding to the area of herpes shown in Fig. 233 ($\times 110$).

had a subacute arthritis of the right knee, with symptoms suggestive of gastric ulcer. *February 11th* there were marked redness and blistering over the painful area on the right side of chest. *February 12th* her tonsils were removed; *February 17th* she was free from pain, and the herpetiform lesions were nearly healed. Cultures from the emulsified tonsils show practically a pure culture

of a slightly green-producing streptococcus. The emulsion from the tonsils in NaCl solution and the cultures in ascites-dextrose broth of streptococci as isolated, and after one animal passage when injected intravenously in 6 dogs and 10 rabbits, produced herpes in 4 dogs and 4 rabbits. After 2 passages one rabbit showed marked herpes of the tongue, while after 3 and 4 passages the streptococci failed to cause herpes in the 3 rabbits injected. Of the 4 guinea-pigs injected intraperitoneally, 1 showed herpes over the left shoulder and over the lumbar region. Three rabbits injected after the strain had been cultivated for one week failed to show herpes.

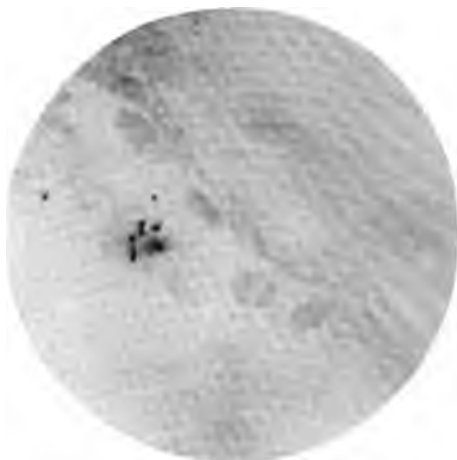


Fig. 235.—Diplococci in a leukocyte within the thrombosed vein shown in Fig. 234 ($\times 1200$).

Rabbit 37.—Injected *February 13th* with 15 c.c. of the emulsion of the tonsil in NaCl solution. *February 16th* it seemed well. Chloroformed. Circumscribed vesicular eruption on the under surface of the skin of the lateral aspect of the head was found. The areas of herpes measured from 0.5 to 1 cm. in diameter, were bilaterally placed, brownish in color, and situated in the skin proper. On cross-section of these areas much fluid exuded. There was suppurative arthritis of the left shoulder-joint. Rather large amount of distinctly turbid, blood-tinged cerebrospinal fluid. *February 19th* cultures of the blood and right Gasserian ganglion gave a pure culture of *Streptococcus viridans*; those from the shoulder-joint showed *Streptococcus viridans* and hemolytic

streptococci; the fluid from the vesicular areas in the skin was sterile.

Dog 217.—*February 13th* a medium-sized white dog was injected intravenously with the growth from 75 c.c. of dextrose-tissue-broth of the original culture from the tonsil. *February 15th* the dog seemed quite well, but tender over the left lower thorax. Chloroformed. On removing the skin a number of circumscribed areas were found showing a hemorrhagic vesicular eruption opposite the eighth and ninth ribs on the left side. On shaving the skin it

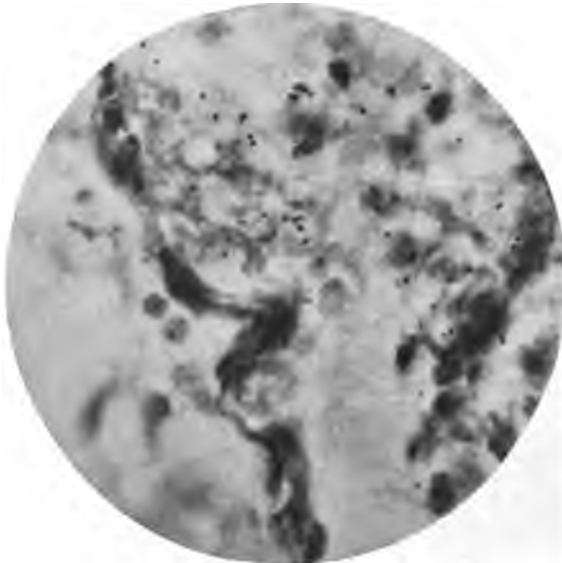


Fig. 236.—Diplococci in the hemorrhagic and infiltrated area surrounding the spinal nerve in the vertebral foramen corresponding to the area of herpes shown in Fig. 233 ($\times 1200$).

was seen that only one of these had blistered (Fig. 237); the others showed only marked hyperemia on the surface of the skin. An area of localized meningitis was found in the cortex between the hemispheres. The eighth and ninth dorsal spinal ganglia on the left side did not show hemorrhages on the surface, but on cross-section showed distinct areas of hemorrhage. Joint fluid was turbid. *February 16th* cultures from the blood, edematous fluid in the vesicles and joint were found sterile. Sections of the eighth dorsal ganglion showed marked congestion, irregular staining of the ganglion-cells, hemorrhage, especially in the sheath, round-

cell infiltration (Fig. 238, *a*), and thrombosis of the accompanying artery (Fig. 238, *b*). The ninth dorsal ganglion showed similar changes, including a thrombosis of its vein. Altogether, 14 Gram-positive diplococci were found in these two ganglia. Serial longitudinal sections of the eighth and ninth dorsal ganglia and of the accompanying nerve-roots showed that the thrombosed vessels were the artery and vein supplying them. Cross-sections of the cord at the level corresponding to the eighth dorsal vertebra showed two areas of hemorrhage in the gray matter in the posterior columns. The nerve-cells surrounding the hemorrhage



Fig. 237.—Herpes of the skin over the left thorax of Dog 217, forty-eight hours after an intravenous injection of the streptococcus from the tonsil of Case 270 ($\times 2\frac{1}{2}$).

stained irregularly, and under high power considerable blood-pigment was found. The blood-vessel accompanying the posterior root just at the exit of the nerve-fibers from the cord and beneath the dura was almost completely plugged by polymorphonuclear leukocytes and other cells (Fig. 239). Prolonged search resulted in the finding of 4 diplococci, 1 free in the vessel, 2 within leukocytes, and 1 in the wall of the vessel on the side of the nerve. Sections at two slightly different levels showed hemorrhages in the posterior nerve-root and a thrombosed blood-vessel under the dura directly opposite the posterior root.

CASE 276.—Severe unilateral herpes zoster involving the left thoracic region, of four days' duration, in a laborer forty-nine years of age. The blistering was marked, the pain intense. The patient thought he had high fever at the onset of the disease, but with the appearance of the eruption it disappeared. He had never had a similar attack. The man was poorly nourished, seemed ill, coughed, and raised small amounts of sputum, but lung findings were negative. *February 22d* tonsil examination showed cryptic tonsils and teeth surrounded by marked gingivitis. Cultures were made from the pus expressed from the tonsils, the material drawn into a pipet from the inflamed gums, the sputum, spinal fluid, blister fluid, and blood. The spinal fluid was clear, but smears from the sediment showed a moderate number of mononuclear cells in which there were a few diplococci. *February 23d* cultures from the blood were sterile; the spinal fluid gave a pure culture of a short-chain streptococcus and a few colonies of streptococci in ascites-dextrose agar. Culture from the tonsils, teeth, and sputum showed chiefly green-producing colonies of streptococci, *Micrococcus catarrhalis*, and staphylococci. Cultures from the clear blister fluid remained sterile; those from the bloody blister fluid gave a few chains of diplococci, a spore-forming bacillus, and staphylococci.

The original cultures from the tonsils, pus-pockets about the teeth, and sputum, in ascites-dextrose-broth were each injected intraperitoneally into one guinea-pig, all three developing herpes. Intravenous injections of cultures of the streptococcus from each of these into one dog, one rabbit, and one guinea-pig each (9 animals in all) were followed by herpes in all but one dog and one rabbit. The pure culture of the streptococcus from the spinal fluid of these animals showed herpes in two rabbits and one dog. After cultivation from one to two weeks, this streptococcus, when injected into five rabbits and two dogs, failed to produce herpes. The streptococcus from the spinal fluid (second culture) produced herpes of the eye and lip and hemorrhage in the corresponding ganglion in a dog.

Rabbit 46.—*February 23d* injected intravenously with the growth from 60 c.c. of ascites-dextrose-tissue broth of a pure culture of *Streptococcus viridans* from the infected gums. *February 24th* chloroformed. Marked herpes of the tongue (Fig. 244), marked areas of localized edema in the lung and mucous membrane of the trachea suggestive of herpes were found. There were a moderate number of localized hemorrhages and edema of the mucous membrane of the stomach, with one ulcer near the lesser curvature

and one in the fundus. Moderate turbidity of the joint-fluid from both knees. Spinal fluid slightly blood-tinged. The Gasserian ganglia appeared edematous, but no distinct hemorrhages could be made out. *February 26th* the blood, spinal fluid, Gasserian ganglia, and joint-fluid showed a large number of green-producing streptococci, and plate cultures from the ulcer in the cardiac end

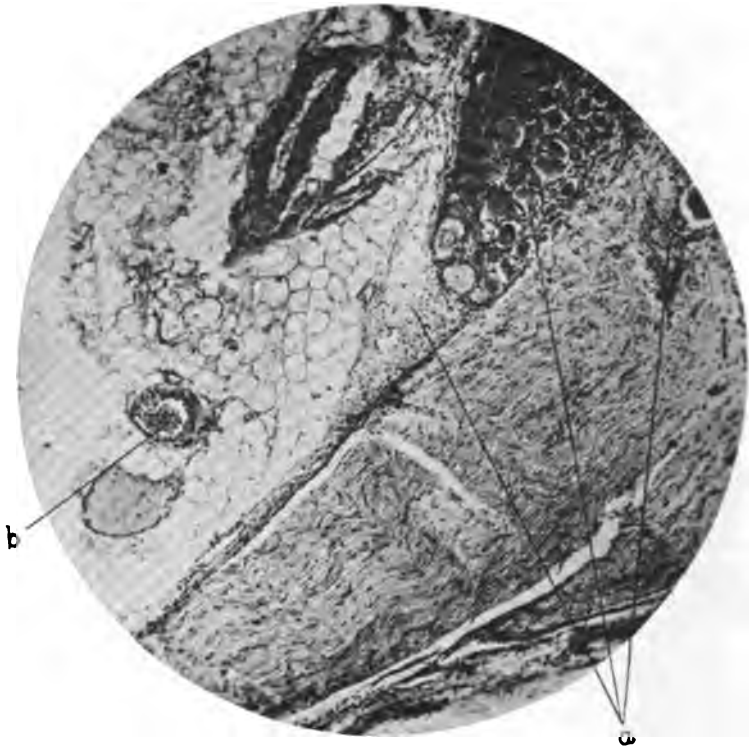


Fig. 238.—Leukocytic infiltration in and surrounding a ganglion (a) and thrombosis of the adjacent artery of the spinal ganglion (b) corresponding to the area of herpes shown in Fig. 237 ($\times 65$).

of the stomach showed 500 colonies of streptococci. Sections of the ganglia of the vagus nerve showed one rather large hemorrhage between the cell-groups, and Gram-Weigert stains showed a few diplococci in the hemorrhagic area. Sections through the ulcerated area at the tip of the tongue showed desquamation, infiltration, and necrosis of the epithelium (Fig. 245, a), slight round-cell infiltration of the underlying muscle (Fig. 245, b), and an aggregation

of leukocytes in a small adjacent blood-vessel (Fig. 245, c). Stains for bacteria showed a large number of Gram-staining diplococci covering the ulcerated area (Fig. 246).

Dog 222.—Medium-sized brown and white dog. *February 23d* injected intravenously with the growth from 90 c.c. of ascites-dextrose-broth of the culture obtained from the tonsil. *February 25th* seemed quite well. Chloroformed. Marked hemorrhage and



Fig. 239.—Thrombosed blood-vessel accompanying the posterior nerve-root within the dura of the ganglion shown in Fig. 238. Note the large number of polymorphonuclear leukocytes ($\times 475$).

edema found in the very lowest portion of the esophagus and the first portion of the stomach. This did not have the appearance of the usual hemorrhages, and the blood was unquestionably diluted with serous fluid. A number of herpetiform lesions could be found under the pleura in the left lung, on the upper surface of the lower lobe. The largest of these measured 0.5 by 4 cm. (Fig. 254, a). The contents of these areas consisted of hemorrhagic edematous

fluid. The sympathetic and vagus ganglia on the right side were embedded in an area of hemorrhage; the spinal fluid was distinctly turbid; no lesions could be found in the spinal ganglia. The liver showed marked congestion; the joint fluids were clear. *February 26th* cultures from the blood, joint fluid, spinal fluid, bile, and

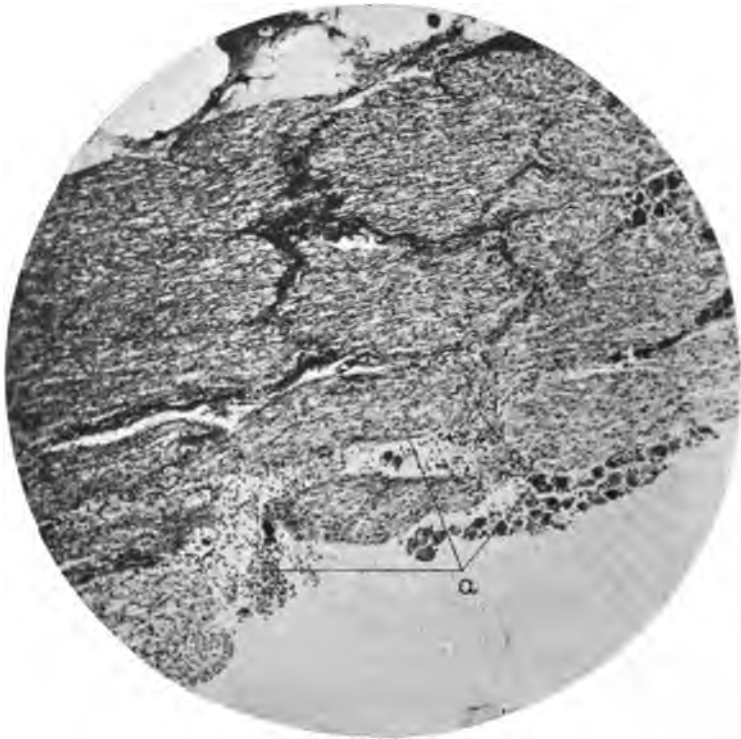


Fig. 240.—Hemorrhage and leukocytic infiltration (a) of a spinal ganglion and of the associated nerve in Rabbit 47, twenty-four hours after an intravenous injection of the streptococcus from sputum in a case of severe thoracic herpes zoster (276) ($\times 60$).

edematous fluid from the herpetiform lesions in the lung were sterile. Sections of the spinal cord, the spinal, sympathetic, and vagus nerves, and a number of spinal ganglia, corresponding to the segment of the lesion of the stomach, showed no changes. The vagus and the sympathetic ganglia showed no gross lesions within their substance, but the capsules and the surrounding areolar tissue

were hemorrhagic. The accompanying blood-vessel of the sympathetic ganglion showed a beginning thrombosis; the thrombus filled one-half the lumen of the vessel, and consisted chiefly of polymorphonuclear leukocytes and large mononuclear cells. Gram-Weigert stains showed diplococci in the hemorrhagic area and a few within the thrombus. Section of the herpes-like area in the lung showed dilatation of capillaries, hemorrhage and edema into alveoli, but with little leukocytic infiltration (Fig. 255).



Fig. 241.—Diplococci and streptococci in the infiltrated area shown in Fig. 240 ($\times 1900$).

Rabbit 47.—Injected intravenously *February 23d* with the growth from 25 c.c. of ascites-dextrose-broth of a culture from the sputum. *February 24th*, found dead. Numerous small punctate hemorrhages in the skin of both ears, some of these distinctly vesicular in character. A ruptured vesicle was found near the inner angle of the right eye and near the juncture of the cornea. The left eye was normal except for some hemorrhage and edema, especially over the lower lid. A number of these had ruptured and glued together the margin of the lids. On the upper left lid a distinct vesicle in the subcutaneous tissue was found. A few lesions were found in the fascia covering the subscapular muscles on the

right side. The spinal cord and ganglia showed no apparent change. The Gasserian ganglia appeared edematous. The middle ears showed a marked exudation, and there was infiltration of pus along the auricular branches of the fifth nerve as they passed along the anterior upper aspect of the temporal bone. Fluid from knee-joints turbid, smears showing leukocytes and diplococci. *February 26th* a large number of green-producing streptococci in pure culture were obtained from the blood, spinal fluid, and Gasserian ganglia. Sections of the left Gasserian ganglion showed small areas of hemorrhage and round-cell infiltration which was most marked in an area at the juncture between the nerve and ganglion. The infiltration extended along the nerve-sheath for a considerable distance (Fig. 240, a). A rather large number of diplococci were found in the infiltrated areas, but not in the normal portion (Fig. 241). Sections of the spinal cord showed no changes, but the left spinal ganglion at a level corresponding to the lesions found in the shoulder showed slight leukocytic infiltration and small hemorrhages.

Pig 59.—A medium-sized white and black guinea-pig was injected intraperitoneally *February 23d* with the growth from 15 c.c. of ascites-dextrose-broth from the sputum. *February 24th*, very ill. Chloroformed. Herpes of the upper lip and inner nostrils was seen only from the under surface of the skin. There were serofibrinous peritonitis and pleuritis; marked hemorrhages of the stomach; marked degeneration and acidity of the liver. There were no gross lesions of the Gasserian ganglia, but sections showed areas of hemorrhages in which were found a number of diplococci. No diplococci could be found in the more normal portion.

Dog 221.—Medium-sized fox-terrier, injected *February 23d* with the growth from 90 c.c. of ascites-dextrose-tissue-broth of the culture from the sputum. *February 25th* lame in the left hind leg. Chloroformed. One herpetiform lesion in the subcutaneous fat over the left shoulder-blade and turbid fluid from the left knee. No other gross findings except a large amount of the usual turbid spinal fluid. *February 26th* cultures from the joint fluids and blood and spinal fluids were sterile. Sections of the cord showed no hemorrhages. The ganglia and associated nerve-roots showed areas of round-cell infiltration in which a few diplococci were found.

CASE 278.—Typical severe thoracic herpes zoster in robust laborer forty-four years of age. The area involved showed numerous small and large blisters, and was supplied by the left seventh and eighth intercostal nerves, and extends from the median line

in the back to the median line in front. The pain, which began three days before, was still severe; blistering occurred one day before. The patient had been well for years except for an attack of sciatica nine months before. Cultures were made from the small amount of pus expressed from the chronically infected tonsils and from the pus aspirated from the depth of several pyorrheal pockets and from the blister fluid. *February 23d* cultures on blood-agar plates from the tonsils and pyorrheal pockets yielded chiefly *Streptococcus viridans*, a few colonies of hemolytic streptococci, and a moderate number of staphylococci. The cultures from the blister fluid were sterile. Smears from the cultures in ascites-dextrose-broth showed very long chains and clumps of streptococci, and larger, short-chained diplococci resembling pneumococci and staphylococci. *March 12th* the patient was examined again and cultures made exactly as before. He was entirely free from pain for ten days and feeling as well as ever. The cultures obtained from the teeth were injected into one rabbit, but it failed to develop herpes. The original culture from the tonsils, containing both staphylococci and streptococci, produced herpes in two out of three rabbits and in one dog. The mixed culture of the streptococcus and staphylococcus obtained from the spinal fluid of the dog showing herpes, produced herpes in two dogs and one rabbit. The broth culture filtrate from the tonsil proved to be sterile. It was injected into two rabbits, neither of which developed herpes. The culture obtained from the tonsil on *March 12th*, after recovery, was injected in three rabbits, one of which developed herpes.

Dog 225.—A large brown and white dog injected intravenously *February 24th* with the growth from 90 c.c. of ascites-dextrose-broth from the tonsil. *February 25th* it seemed ill and in pain. Slight pressure over lower thorax caused animal to yelp. No visible changes of the skin. No herpes about the mouth or eyes. *February 26th* seemed somewhat better than the day before. No herpes could be made out, but the skin over the right lower thorax was distinctly hyperemic. *February 27th*, 9 A. M., extremely tender over the thorax. There were two large, bluish-red, edematous areas, approximately 5 x 8 cm., in the skin over the lateral and lower aspects of the thorax. Slight pressure here caused the dog to yelp. On watching the dog for some hours the pain seemed to be especially severe at intervals of from ten to thirty minutes, during which time it cried out and rolled from side to side as if in great pain. The animal was alert mentally, and when petted or spoken to kindly wagged its tail. The condition grew worse;

breathing labored. A number of blisters appeared over the lower thorax. The animal was now chloroformed and examined at once. The skin over the lower and anterior portion of the thorax on both sides showed marked hemorrhage, edema, swelling and blistering over areas approximately 6 x 10 cm., the long axis being parallel with the ribs. These were surrounded by numerous smaller herpetic lesions (Fig. 242), some of which did not involve the thick, hair-covered, overlying epidermis. The edema and infiltration of the large areas extended through the wall of the chest over a small area (3 cm.) on both sides, where the peritoneum was blistered. All gradations in the character of the fluid in the lesions, from a clear serous fluid to a deeply blood-tinged and bloody, purulent fluid, were found. The larger areas appeared infected. It was

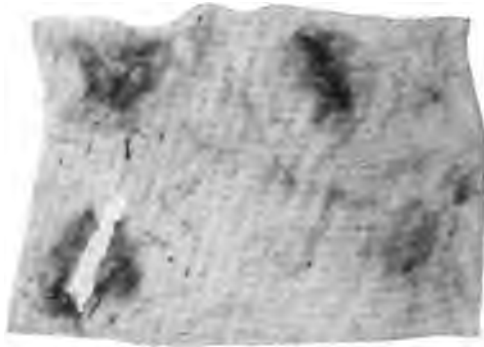


Fig. 242.—A number of the smaller areas of herpes of the skin over the thorax of Dog 225, seventy-two hours after an intravenous injection of the streptococcus from the tonsil in a case of severe thoracic herpes zoster (278) (natural size).

impossible to shave away the hair over these areas without causing the blisters to rupture. Herpetiform lesions were also found over the lower portion of the abdomen, of the prepuce, and under the right shoulderblade. The peritoneal cavity contained a moderate amount of turbid fluid. The stomach in extreme spasm contained no food, but a moderate amount of bloody mucus, which reacted faintly acid to litmus. The mucous membrane of the fundus and pyloric end of the stomach showed edematous, raised, and opaque areas, in which were found many small hemorrhages and a number of superficial erosions. These areas had the typical appearance of herpetiform lesions. The liver showed marked congestion and mottling. The wall of the gall-bladder contained four circumscribed, edematous, hemorrhagic areas, resembling herpes.

The kidneys appeared normal except for several circumscribed opaque, edematous areas resembling infarcts. The lungs appeared normal, except that there were altogether seven subpleural, circumscribed, elevated collections of bloody serum having the appearance of vesicles. The myocardium was opaque and showed a number of small infarcts (2 x 5 mm.). The left auricle contained two herpetiform lesions at the juncture of the auricular appendix and the main body of the auricle. One of these appeared to involve the sino-auricular node. The spinal ganglia in the lower cervical and upper dorsal region, especially on the right side, were embedded in dark clotted blood. The hemorrhagic areas here were often fused, giving the appearance of an acute diffuse pachyleptomeningitis. Similar but smaller hemorrhages were found around the ganglia and cord in the lumbar region. The vagus and right sympathetic ganglia were surrounded by small hemorrhages and appeared edematous. The brain, vagus and sympathetic nerves, the thyroid, adrenals, pancreas, the mucous membrane of the mouth, eye, and esophagus, the spleen, testicles, and extremities, appeared normal. *February 28th* cultures were made from the brain substance, the herpetiform lesions in the gall-bladder, and the lung; the bile and joint fluid were sterile. The cultures from an infarct in the myocardium, from the blood, and from two subcutaneous lesions showed *Staphylococcus aureus* only. The more marked lesions in the skin showed staphylococci, a large bacillus, and streptococci. The peritoneal and spinal fluids yielded staphylococci and streptococci. Ascites-dextrose-agar plate cultures of the emulsified tissue of two of the herpes-like areas in the stomach gave 30 and 50 colonies of streptococci. Section of the involved skin showed edema, leukocytic infiltration, and hemorrhage, especially of the deeper layers. The squamous epithelium in portions was raised, desquamated, and in some areas sloughed away (Fig. 243). The deeper cuboidal cells were everywhere intact. Gram stains showed clumps of cocci in diplococci and short chains, and a few bacilli in areas showing leukocytic infiltration. In the intercostal and abdominal muscles from the involved area were marked interstitial infiltration and hemorrhage. The spinal ganglia and posterior nerve-roots corresponding to the areas of herpes of the thorax were surrounded by marked hemorrhages and leukocytic infiltration which extended into the sheath. The associated blood-vessels showed partial thrombosis. A moderate number of diplococci and a few round single and clumped cocci were found in the hemorrhagic area showing blood-pigment. Longitudinal sections of the subcu-

taneous nerves running into the involved area disclosed no changes except infiltration of the sheath in the involved area. Proximal to this point there were no changes. The vagus ganglion was surrounded by hemorrhages and leukocytic infiltration, chiefly of the capsule of the ganglion and nerve-sheath for a short distance (Fig. 256). Diplococci were found in the hemorrhagic area. The

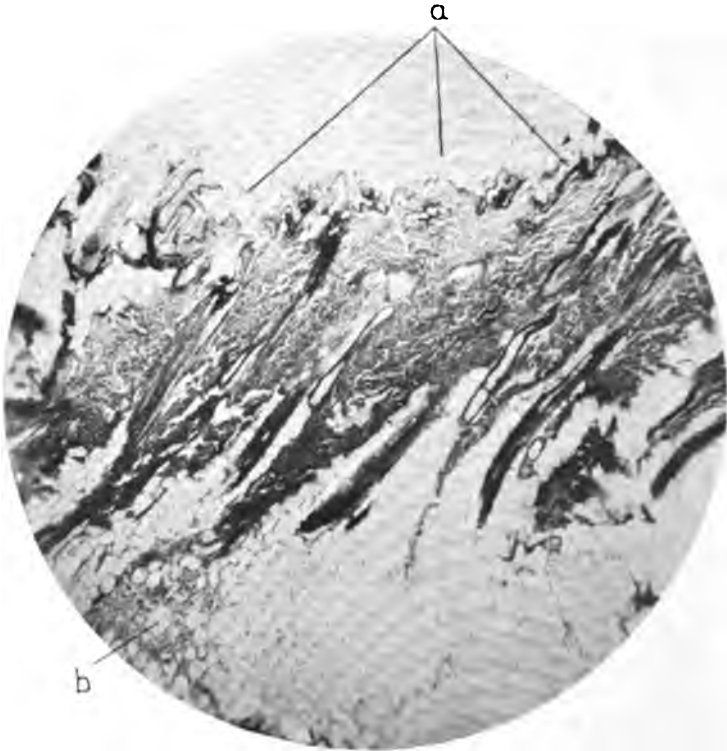


Fig. 243.—Section of the skin through the area of herpes (Fig. 242) over the thorax in Dog 225, seventy-two hours after an intravenous injection of the streptococcus from the tonsil in Case 178. Note the desquamation of the epidermis (a) and the leukocytic infiltration (b) ($\times 35$).

sympathetic ganglion showed no changes except slight hemorrhage beneath its sheath. There were no changes in the vagus and sympathetic nerves remote from the ganglia. The areas resembling herpes under the pleura in sections showed extravasation of blood into the distended alveoli. The blood-corpuscles in the alveoli were separated and did not fill them completely.

CASE 281.—Recurring herpes zoster involving the upper and outer aspects of the right thigh in a nervous woman forty years of age. The attacks had occurred yearly during early spring, and usually were not associated with distinct tonsillitis or other apparent infection. Three years before she had had a severe attack of bilateral thoracic herpes zoster, and since then had had more or less distress after meals, suggesting duodenal ulcer. The attack here described began ten days after the onset of a typical attack of diphtheria. Seven days after the temperature was normal (two days before the attack described), and after the throat cultures had failed to show diphtheria bacilli, the patient began to have pain in the outer aspect of the thigh, followed by redness and blistering on the third day after appearance of pain. *February 25th*: The tonsils small but red; from the crypts was expressed a small amount of fluid pus. Cultures were made from the pus expressed from the tonsil and from the blister-fluid. *February 26th*, blood-agar plate cultures gave a large number of green colonies of streptococci and *Micrococcus catarrhalis*. Loeffler's serum slants yielded no diphtheria bacilli. Smears from the ascites-dextrose-tissue-broth cultures showed pure culture of a short-chained streptococcus. The cultures from the blister-fluid were negative. *March 3d* the patient had fully recovered; pain was absent; blistered areas nearly healed. Cultures were again made from the tonsils. *March 4th* blood-agar plates inoculated with material from tonsils showed, as before, many green colonies of streptococci; a few colonies of hemolytic streptococci and *Micrococcus catarrhalis*, but smears from the broth cultures showed much longer chains of streptococci than those in the former culture. The primary culture from the tonsil pus during the attack was injected into two dogs and two rabbits. Only one rabbit developed herpes. The culture of the streptococcus obtained pure from the spinal fluid of this rabbit was injected into six rabbits and one dog, of which four rabbits developed herpes. The result in the dog was negative. The filtrate of the broth culture, thought to be sterile, but from which a few streptococci were isolated later, produced herpes of the right lower abdomen and outer aspect of the right thigh, associated with hemorrhage of the corresponding ganglion in the one rabbit which was injected (see experiment on Rabbit 56), and herpes of the upper lip in one of two dogs previously injected with the growth from the tonsil. A portion of the above filtrate was refiltered and again injected intravenously into a rabbit of

the same size. No herpes developed, and cultures made from the sediment of a centrifuged portion remained sterile. The cultures made after the patient had recovered failed to produce herpes in the one rabbit injected.

Rabbit 62.—Injected intravenously *February 26, 1915*, with the growth from 45 c.c. of ascites-dextrose-tissue-broth from the tonsil. *February 28th*, seemed ill and as if in pain. Marked herpes of the skin of both ears. Chloroformed. The skin of both ears was studded with numerous small hemorrhages and vesicular areas (1 to 7 mm. in diameter). These bear no relation to the site of the injection. A number of the vesicular areas had ruptured, and the dried serum covered the area. On cutting across a number of these a relatively large amount of serosanguineous fluid exuded. There was herpes of the skin over the upper aspect of the thighs (more marked over right) and lower abdomen (Fig. 233). The herpes followed the distribution of the cutaneous nerves. The mucous membrane of the tongue was edematous at points, and a few ruptured blisters were found along the margin. The duodenum showed four edematous hemorrhagic areas 1 cm. beyond the pyloric ring. Three of these were distinctly vesicular, while the fourth was a small submucous fading hemorrhage. The gall-bladder wall contained six small, whitish, edematous areas over the fundus. The kidneys were pale, and presented a peculiar appearance (Fig. 251). The capsule was raised in areas by clear fluid which escaped on section. When the capsule was stripped, much fluid exuded and some of the edematous opaque areas were found to extend into the cortex for a considerable distance. The cut surface was very moist. The medulla was grayish red. The mucous membrane of the pelvis was edematous and blistered in areas. The mucous membrane of the ureters and bladder showed no changes. The pericardial sac contained a moderate amount of turbid fluid; the parietal layer was edematous. The myocardium was mottled grayish-red; the endocardium, normal. The lungs showed a peculiar mottled appearance, but no distinct vesicles could be found. The right Gasserian ganglion was edematous. The right auriculotemporal nerve was surrounded by pus. The drum-membrane and lining of the middle ear on this side were edematous and hemorrhagic, and the cavity contained thin pus in which a number of diplococci were found. The left Gasserian ganglion and middle ear presented a similar appearance. The meninges were dry; the brain, cervical and dorsal ganglia appeared normal. In the lumbar region extradural hemorrhages sur-

rounded the posterior nerve-roots and ganglia. No gross hemorrhages could be made out on the freshly cut surface of the ganglia and cord. The sympathetic ganglion on the right side and vagus ganglion on the left side were surrounded by hemorrhages. Those on the opposite side showed less change. Diplococci showing disintegration were found in the hemorrhagic area surrounding the left vagus ganglion (Fig. 253). The stomach, liver, pancreas, spleen, lymph-glands, eyes, thyroid, and joints were normal. *March 1st*, cultures from spinal fluid, Gasserian ganglion, pericardial fluid, kidney, and blood yielded short-chained, green-producing streptococci only. Sections of the cord, nerve-roots, and ganglia corresponding to the area of herpes showed slight round-



Fig. 244.—Marked herpes of the tongue in Rabbit 46, twenty-four hours after an intravenous injection of the streptococcus from a pyorrheal pocket in a case of severe thoracic herpes zoster (276) ($\times 2\frac{3}{4}$).

cell infiltration and hemorrhages of the posterior horn, of the corresponding ganglia and associated sheaths, and thrombosis of the accompanying vessels (Fig. 234). Diplococci here were easily found. Sections of a herpetiform lesion of the skin of the ear showed sloughing of the epidermis, round-cell and red blood-cell infiltration, and a few diplococci in the cutis vera.

Sections of kidney stained by hematoxylin and eosin exhibited circumscribed areas of edema. The parenchymatous cells of the tubules were swollen, the protoplasm was granular and vacuolated, the nuclei stained poorly, some retaining their form, others showing disintegration. Some of the glomeruli in these areas were distended, the cells separated, and the spaces filled with finely gran-

ular fluid. The adjacent areas appeared normal, except for congestion of the blood-vessels, small hemorrhages, and compression of the tubules and the glomeruli. These areas extended well through the cortex. The contrast between the edematous cells with poorly stained nuclei and the intermediate portion of compressed, well-stained cells was striking. The medullary portion was normal except for marked congestion of the blood-vessels (Fig. 252). When stained for bacteria, many diplococci were found in radiating lines chiefly between and within the cells of the convoluted tubules of the areas showing the herpes. The more normal portions and glomeruli did not show bacteria.

Rabbit 56.—*March 2 and 3, 1915*, large white Belgian hare injected intravenously with 10 and 5 c.c. of the filtrate of the streptococcus culture in ascites-dextrose-tissue-broth from the spinal fluid of Rabbit 62. *March 6th* it seemed well. Chloroformed. No gross lesions were found except several areas of herpes, 0.5 to 1 cm. in diameter, of the deeper layer of the skin over the left lower abdomen and over the upper and outer aspect of the right thigh. A thorough search for lesions of the corresponding spinal ganglia failed to show gross lesions, but they were saved for microscopic sections. *March 8th* the blood, spinal fluid, and lung sterile. Sections of the spinal ganglia, nerve-roots, and pia-arachnoid membrane showed distinct hemorrhages and round-cell infiltration. The associated larger vessels were surrounded by leukocytic infiltration. Gram-Weigert stains showed diplococci in the infiltrated areas.

CASE 368.—Lobar pneumonia with marked herpes of the lips, nostrils, and left side of the face of a young man. *March 22d*, the fifth day of the disease, cultures were made from the tonsils and sputum. *March 23d*, cultures from the tonsils and washed sputum gave a large number of green-producing colonies resembling pneumococci. The former yielded also hemolytic streptococci and *Micrococcus catarrhalis*. The broth culture gave chains of a diplococci. The culture from the sputum in ascites-dextrose-broth was injected into one dog and one rabbit. The former developed herpes of the lip and tongue; the latter, of the left side of the face and head, and bronchopneumonia forty-eight hours after the injection. The culture from the tonsil was also injected into one dog and one rabbit. The former developed herpes of the lip; the latter, herpes of the conjunctiva of the left eye, and of the skin over the left side of the face and thorax. The Gasserian ganglion of the dog injected with the tonsil-strain showed areas of hemorrhage

(Fig. 250, *a*) and round-cell infiltration (Fig. 250, *b*). The cultures of the strain isolated from the spinal fluid of the rabbits injected with strains from the sputum and tonsil failed to ferment inulin, but otherwise closely resembled pneumococci.

CASE 382.—Acute gangrenous thoracic herpes zoster in a man fifty-six years of age. Beginning *March 30, 1905*, the patient had pain in the right lower costal nerve for a week. The day before

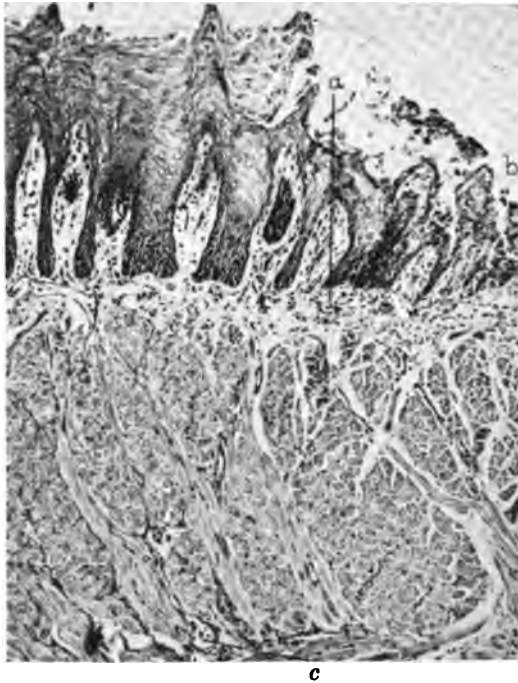


Fig. 245.—Section through a herpetic lesion at the tip of the tongue shown in Fig. 244. Note the hemorrhage and cellular infiltration (*a*), the ulceration (*b*), and the beginning thrombosis of an adjoining blood-vessel (*c*) ($\times 75$).

a rash had appeared over the tender areas, and during the night a number of small blisters appeared. No other complaint except nasal catarrh during the past year. Leukocytes, 10,000. Hemoglobin, 90 per cent. Tonsils small, cryptic, and covered by anterior pillars. By making pressure outside of the left tonsil a small-sized abscess was ruptured. Cultures were made from the pus obtained. *April 2d* cultures on blood-agar plates yielded chiefly *Streptococcus viridans*, a few hemolytic streptococci, and staphylococci.

Injection of the growth in ascites-dextrose-broth culture from the tonsil into two rabbits produced in one herpes of the left margin of the tongue, marked herpes of the conjunctiva of the right eye, moderate of the left, and herpes of the left side of the thorax; in the other, herpes of the lateral aspect of the abdomen. The pure culture of streptococci obtained from the spinal fluid of these rabbits produced herpes in two of four rabbits injected; in one, of the left thorax; in the other, of the lip, tongue, and left side of the face. During the night following the examination the symptoms became much worse, and on *April 7th* Dr. Kretchner, who kindly referred the patient to us, reported that the patient was suffering excruciating pain and that there were numerous ulcers at the site of the lesions. It would seem that, during the examination or later, there occurred a new invasion of the bacteria, which proved to have affinity for the posterior ganglia, converting a mild attack into a severe one.

CASE 391.—Acute herpes zoster in a man forty-three years of age (merchant). Forty-eight hours after taking five grains of calomel, which was thought to have salivated him, the herpes began in the left lower lip, then spread to the left side of the tongue, left buccal surface, and thence to the left side of face, including the left ear. The pain was intense for several days before the eruption appeared, also throughout the attack and afterward,—four weeks in all,—although the herpes had healed. There were marked swelling and edema of the involved areas, especially of the ear, which resembled erysipelas. This was thought to be a secondary infection due to streptococcus, and antistreptococcus serum was given. A marked neurasthenic state developed after the herpes began. The man had had pyorrhea for years. *April 16th* the tonsils were found to be small, but hyperemic and visibly infected. There was pyorrhea, especially about lower incisors. Cultures were made from the small amount of pus expressed from both tonsils and from that aspirated from the pyorrheal pockets. *April 20th* blood-agar plates made from the cultures in ascites-dextrose-broth inoculated with the pus from the tonsils and teeth showed *Streptococcus viridans*, staphylococcus, and a few colonies of influenza bacilli. The original culture in ascites-dextrose-broth from the pyorrheal pocket was injected intravenously into two rabbits and one dog. One rabbit and the dog developed herpes. In the rabbit the herpes was situated under the eye and left lateral thorax; in the dog, in the right upper lip and tongue. The culture from the tonsil was also injected into two rabbits and one dog;

of these, only one rabbit showed herpes, the skin being involved over the right hip. The relatively high incidence of herpes following these injections is in keeping with the fact that, while the acute symptoms had subsided, the pain was still present when the cultures were made.

Completely negative results were obtained following intravenous injection of the cultures from the tonsils in a case of recurrent herpes of the mouth, and with the cultures obtained from the nasal discharge in a patient suffering from acute rhinitis associated with simple herpes of the lip.

RESULTS OF THE CULTURES

Cultures have been made in 11 cases of herpes. In five of these there was marked thoracic herpes zoster; one was a severe herpes of the left side of the face and left ear; three were recurring (one involving the left arm, one the outer and upper aspect of the right thigh, and the other the mucous membrane of the mouth); in one there was a marked herpes of the lips and left side of the cheek during pneumonia; in another, a mild herpes of the lip during an attack of acute rhinitis. In no instance was there acute tonsillitis. The pus-pockets found in the tonsils were small. All but four patients had pyorrhea. The patients included one woman, forty-five years old, nine men from forty to fifty-six years old, and one young man. The cultures from the tonsils (all of which contained pus), sputum, and pyorrheal pockets showed a preponderance of moist, green-producing colonies of a non-encapsulated, Gram-staining, short-chain, often lanceolate streptococcus. The cultures of the clear blister-fluid in human herpes were usually sterile, or showed a few colonies of a large staphylococcus; but in one patient (Case 276) cultures from a hemorrhagic blister fluid showed a few colonies of a green-producing streptococcus, a large Gram-staining, spore-forming bacillus, and staphylococci. Cultures from the spinal fluid and blood were made in only one case. The former showed a pure culture of the streptococcus; the latter remained sterile. The fermentative powers of various sugars in broth tested in seven of these strains proved to have affinity for the ganglia. All but one produced acid in saccharose; all but two in

salicin; three fermented raffinose, and two, mannite; none fermented inulin. In short, these streptococci had the features of a pneumococcus, except high virulence, capsule, and inulin fermentative powers (Fig. 257). At times there were found in the tonsils and pyorrheal pockets a few hemolyzing colonies of streptococcus, and frequently small, dry, and slightly green-producing colonies of a smaller streptococcus. This was true both in blood-agar plates made directly, and in those from the ascites-dextrose-



Fig. 246.—Diplococci covering the base of herpetic ulcer of the tongue shown in Figs. 244 and 245 ($\times 1200$).

broth cultures. *Micrococcus catarrhalis* was commonly present in the usual numbers. The cultures differed from those of the tonsils in other diseases in that they showed an unusually large number of staphylococci. Anaërobic cultures on blood-agar were not characteristic.

RESULTS OF INTRAVENOUS INJECTIONS

In the table is given a summary of the results (see table) of the injection of the strains when first isolated, after cultivation for a

time, and after animal passage. Sixty-one animals were injected with 11 strains as isolated. Of these, 70 per cent. showed herpes of the skin (Figs. 232, 233, 237, and 242); 15 per cent., herpes of the eyelids—a total average of experimental herpes in 75 per cent. The lesions varied from those very small—just recognizable—to others very large and marked (Dog 225).

LOCALIZATION OF STREPTOCOCCI FROM HERPES ZOSTER

SOURCE OF STREPTOCOCCI		Strains	Animals Injected	PERCENTAGE OF ANIMALS SHOWING LESIONS IN																		
				Appendix	Stomach	Duo- denum	Ul- cers	Gall-bladder	Pancreas	Intestines	Joints	Endocardium	Pericardium	Myocardium	Muscles	Kidneys	Lungs	Skin	Tongue	Eyes	Parotids	
																						Hem- or- rhage
Herpes zoster	When isolated	11	61	10	29	8	16	2	8	11	5	11	5	11	5	11	5	21	70	13	13	..
	Later	6	15	0	13	7	7	13	7	60	7	0	20	40	7	20	7	20	7	0	13	..
	After animal passage	4	7	..	28	10	43	..	14	..	28	..	43	28	14

In some instances the tendency of the strains from the apparent atria of infection to produce herpes was so marked that it occurred in nearly all animals injected intravenously, and in some it developed even after intraperitoneal injection. Thus in one patient (Case 276) the original cultures in ascites-dextrose-broth from spinal fluid produced herpes in a guinea-pig, rabbit, and dog. The pure cultures of the streptococcus from the spinal fluid of these animals produced herpes in two rabbits and one dog. That the herpes is due to the streptococci injected, and not to some ultra-microscopic organism, is indicated by the fact that sterile filtrate of these cultures failed to produce the disease. Moreover, when the characteristic affinity was marked, only a few streptococci were sufficient to produce the disease. Thus in one rabbit herpes of the skin with lesions and streptococci in the corresponding spinal ganglion (Rabbit 56) followed injection of what was thought to be a sterile filtrate, but which later, by centrifuging and making cultures from the sediment, was proved to contain a few living streptococci (probably not more than 10). A portion of the filtrate was again filtered and injected. It was now proved to be free from

streptococci, and, accordingly, it failed to produce herpes. Injection of the emulsion in NaCl solution of the extirpated tonsil at the outset of an attack (Case 270; Rabbit 37), as well as the original cultures in broth, containing a mixture of bacteria, was followed by herpes proved to be due to streptococci.



Fig. 247.—Herpes of the tongue and of the mucous membrane about the teeth and lips in Rabbit 33, twenty-four hours after intravenous injection of the streptococcus from the tonsil in a case of recurring herpes (267) ($\times 2\frac{1}{4}$).

The lesions were usually unilateral, especially after the injection of small doses, although after the injection of large doses bilateral herpes occurred quite often. In some instances the location of the herpes in the animals corresponded quite closely to that in the patients from whom the cultures were obtained (Case 281; Rabbits 62 and 56; Case 368; Dog 299).

The table shows further that after the streptococci are cul-

tivated on artificial media (seven to fourteen days), and after animal passage (two to five), they lose largely the power to produce herpes; it occurs in only 7 and 28 per cent. of the animals injected. Likewise, the cultures made from the presumable infection-atrium seven to ten days after recovery produced herpes in only one of nine rabbits and three dogs which were injected. In the patient (Case 391), however, who continued to have severe pain (postherpetic neuralgia) four weeks after the lesions of the

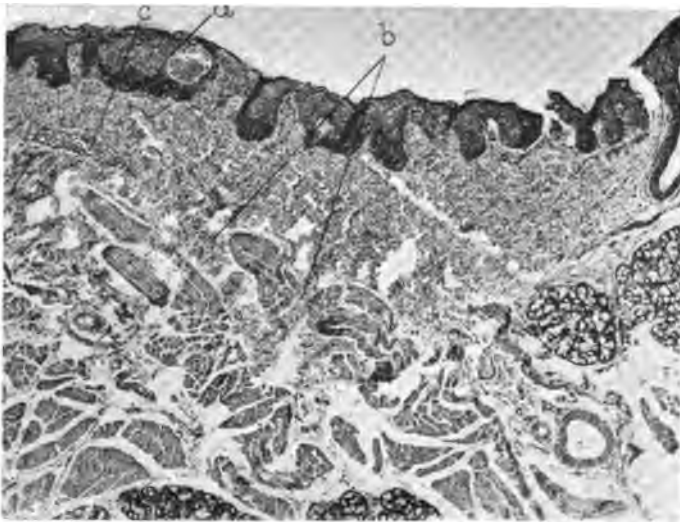


Fig. 248.—Section through a herpetic area of the lip of the rabbit shown in Fig. 247. Note the hemorrhage in the epidermis (a) and deeper layers of the skin (b), and the thrombosed blood-vessel (c).

skin had healed still harbored streptococci, which produced herpes in most of the animals injected.

The posterior roots or ganglia corresponding to the area of herpes of the skin (Figs. 232, 233, 237, and 242) nearly always showed hemorrhages and edema. Smaller hemorrhages were usually found about the neighboring ganglia in those animals with severe herpes, but in which the corresponding area of the skin was free from herpes. The hemorrhage at times extended for a short distance along the sheath of the spinal nerve, but the intercostal

nerves and the cutaneous branches remote from the lesions in the ganglia and skin showed no gross or microscopic changes. The hemorrhages about the ganglia and posterior root at times extended into the loose connective tissue of the external and posterior portion of the dura, presenting the picture of an external pachymeningitis. Herpes of the skin of the ears of rabbits, when present, was usually bilateral, and was nearly always accompanied by herpes of the tongue. In two rabbits with marked herpes of the external ears there were found what appeared to be herpes of the drum and middle ear, and infection extending from the Gas-

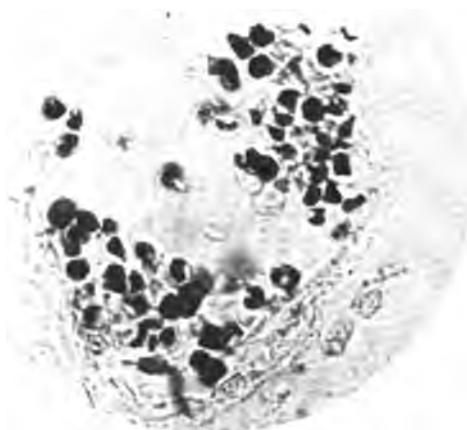


Fig. 249.—Diplococci in the thrombosed blood-vessel shown in Fig. 248 (c) ($\times 1200$).

serian ganglia along the auricular nerve. Herpes of the face, eyelids, and tongue was usually accompanied by hemorrhage of the Gasserian ganglion.

Herpes of the viscera occurred chiefly after injection of large doses in animals, showing marked bilateral herpes of the skin. In some instances, however, it occurred without herpes elsewhere (Case 276 and Dog 222). Herpes has been observed in the lung and pleura (Fig. 254), peritoneum, gall-bladder, mucous membrane

of the stomach and duodenum, of the kidney (Fig. 251) and visceral pericardium. Herpes of the viscera was always accompanied by hemorrhage and edema about the ganglia of the vagus or sympathetic nerve, or both. Lesions in the vagus and sympathetic ganglia were not found where visceral herpes was absent.

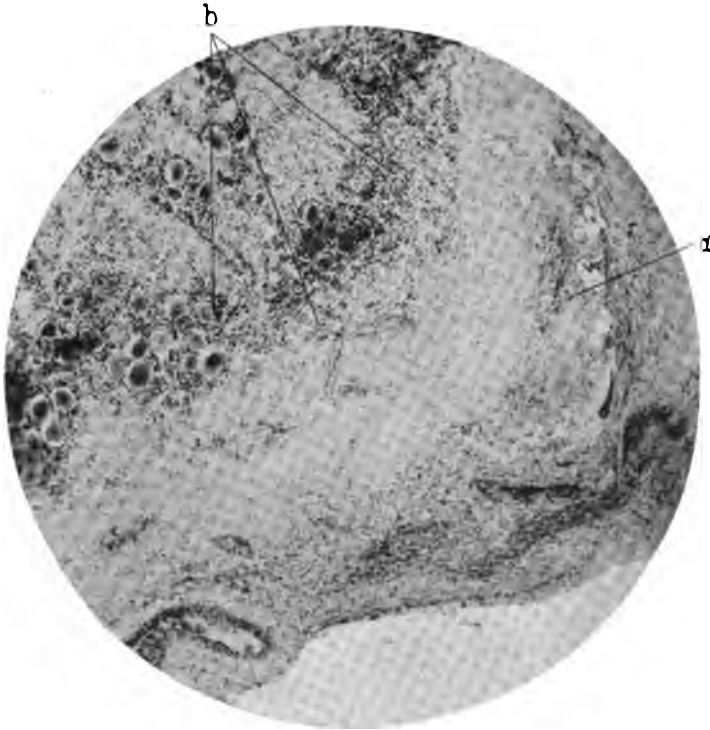


Fig. 250.—Hemorrhage (a) and round-cell infiltration (b) of the Gasserian ganglion in Dog 299, forty-eight hours after an intravenous injection of the streptococcus from the tonsil in a case of lobar pneumonia with marked herpes of the lip and cheek (368) ($\times 60$).

Cultures made in animals after injection showed that the streptococci tended to disappear from the blood. Sixty per cent. of the animals survived the injection. This afforded opportunity to study the rôle played by the bacteria in the production of the disease. Routine cultures were made of the spinal fluid, the hemorrhagic area about the ganglia, the blood, blister-fluid, and joint-

fluid. The spinal fluid showed quite a characteristic turbidity, which was due chiefly to mononuclear cells. The cultures of the spinal fluid and hemorrhagic ganglia nearly always showed a larger or smaller number of colonies of the characteristic streptococcus, even when the blood and other cultures were sterile. In fact, this was common after injections of the primary cultures from the focus containing, in addition to streptococci, staphy-



Fig. 251.—Herpes of the kidney of Rabbit 62, forty-eight hours after an intravenous injection of the streptococcus from the tonsil in Case 281. Note the numerous vesicles under the capsule ($\times 214$).

lococci. The streptococci from the spinal fluid in these animals showed a marked tendency to produce herpes when injected the second time, but subsequent injections rarely produced herpes. Cultures from the herpetiform lesions in the skin, which showed no hemorrhage, and in animals that survived the injection, were usually sterile; while those from the marked lesions with hemorrhage, and at times necrosis and beginning gangrene (Dog 225),

showed the organism injected together with staphylococci and bacilli. Localized meningitis has been observed once. The occurrence of lesions in the other organs corresponds quite closely to the average incidence of lesions in these organs following the injection of streptococci from a wide range of sources.²³

MICROSCOPIC ANATOMY OF THE LESIONS

Microscopic examination of the milder herpetic areas in the skin showed separation of the cells, desquamation, and, usually,

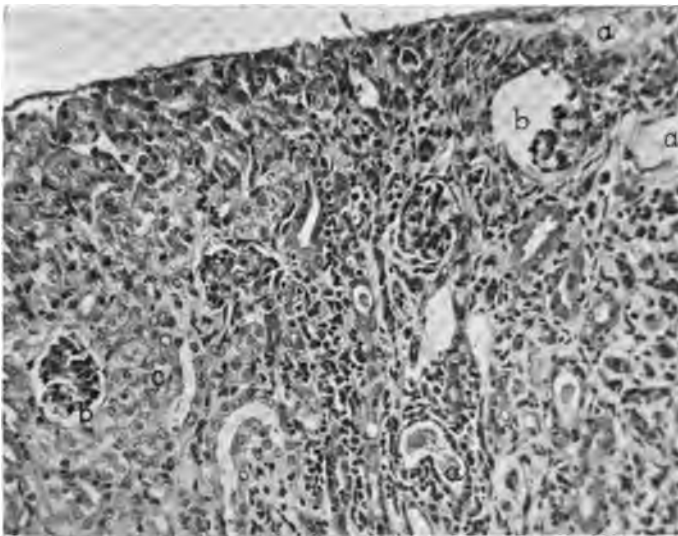


Fig. 252.—Section of the kidney shown in Fig. 251. Note the edematous areas (a), the compression of the glomeruli (b), and the swollen epithelium in the tubules with poorly staining nuclei (c).

slight round-cell infiltration. Bacteria were not found in these. The marked lesions (Fig. 243) showed desquamation of the epithelium of the epidermis, hemorrhage, marked leukocytic infiltration, and at times thrombosed blood-vessels (Fig. 248, c). In these staphylococci, streptococci, and bacilli were found. The sections in herpes of the tongue and lip showed sloughing of the mucous membrane, partial or complete thrombosis of blood-vessels, marked hemorrhage of the muscular layer, and leukocytic infiltra-

tion (Fig. 248). The blistered epithelium of the tongue sloughed promptly; the ulcerated base showed a large number of streptococci in all the sections examined (Figs. 245 and 246). The lesions in the ganglia and adjacent nerve-trunks consisted usually of small areas of hemorrhage and round-cell infiltration immediately surrounding the capsule of the ganglia or the associated nerve-sheath, and around the accompanying blood-vessels (Figs. 234, 236, 238, 239, 240, 250, and 256). The blood-vessels of the ganglia and posterior root usually showed partial or complete thrombosis (Figs. 234, 238, and 239), the thrombi consisting of polymorpho-

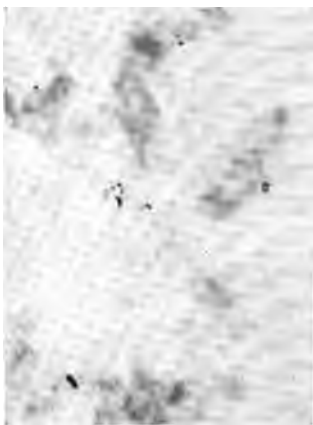


Fig. 253.—Diplococci in the hemorrhagic vagus ganglion of Rabbit 62, showing herpes of kidney shown in Fig. 251 ($\times 1200$).

nuclear leukocytes and large mononuclear cells and fibrin (Fig. 239).

Serial sections in one instance showed that the thrombus in the artery to the ganglion extended for a considerable distance along the posterior root and under the dura. Diplococci, often in large numbers, have been found in the hemorrhagic and infiltrated areas of the spinal, vagus, and sympathetic ganglia, but not in the portions free from changes nor in the normal ganglia (Figs. 236, 241, and 253). The bacteria have been found in the thrombosed blood-vessels accompanying the lesions of the ganglia and posterior horns,

and in the peripheral lesions in the herpes of the lip and tongue (Figs. 235 and 249). It must not be supposed that the finding of diplococci in the hemorrhagic infiltrated areas about the ganglia was a part of the general invasion, because they were absent in the portions of sections showing no change, and present in many instances in the lesions in animals seemingly well and in which the blood was sterile. Longitudinal sections of the vagus, sympathetic, intercostal, and cutaneous nerves, and of the accompanying sheaths remote from the lesions in the ganglia or skin showed no changes

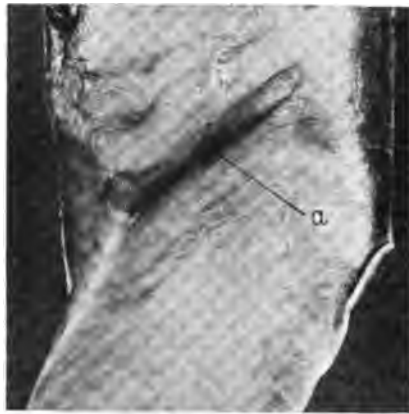


Fig. 254.—Herpes (a) of the lung in Dog 222, forty-eight hours after an intravenous injection of the streptococcus from the tonsil of Case 276 ($\times 1\frac{1}{4}$).

nor bacteria. Sections of the spinal cord in a few instances showed hemorrhage and round-cell infiltration in the posterior columns.

SUMMARY AND GENERAL DISCUSSION

The streptococcus found by us, which has such marked affinity for the posterior root ganglia, resembles morphologically the diplococci found in the Gasserian ganglia by Sunde. The cells found in the spinal fluid in the animals injected are similar to the cells in the spinal fluid in herpes in man (Schottmüller²⁴). The common occurrence in the spinal fluid of the streptococci in pure culture having affinity for the ganglia even when mixed cultures

were injected is in accord with the finding of the streptococcus in the spinal fluid in one of our cases, and in those of Achard and Loeper, Vidal and Brissaud-Siccard (cited by Oppenheim).

The occurrence of relatively slight lesions in ganglia without peripheral herpes adjoining those showing marked lesions, accompanied by herpes; the finding in the atrium of infection of bacteria having affinity for the posterior roots and ganglia in the patient who continued to have pain after the lesion of the skin had healed, and

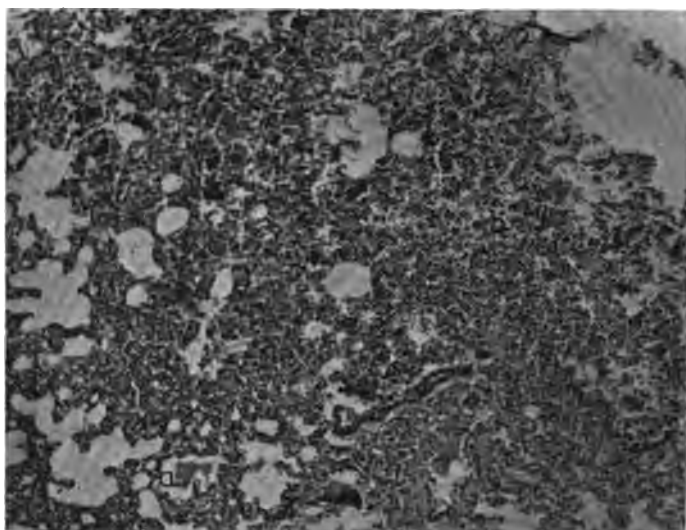


Fig. 255.—Section of the lung through the herpetic area shown in Fig. 254. Note the edematous fluid (a) and the hemorrhage (b) in the alveoli, and the absence of the pleura.

not in those free from pain, suggests strongly that the pain in post-herpetic neuralgia and allied conditions is due to active but slight infection of the ganglia or posterior roots. That these pains are not always due to scar tissue is certain because Head and Campbell have found that ganglia corresponding to the area of herpes zoster may be largely replaced by connective tissue, without the patients suffering pain. The occurrence of herpes zoster in patients who have ulcer of the stomach (Case 281) or empyema is probably not a reflex arc effect or infection of the ganglia by way

of the nerve lymphatics, as believed by Orr and Rowe,²⁵ but is due to a hematogenous infection from a focus harboring streptococci that have an elective affinity for the structures involved. The occurrence of ulcer of the stomach in 8 per cent. of the animals proved to be due to local streptococcal infection in the mucous

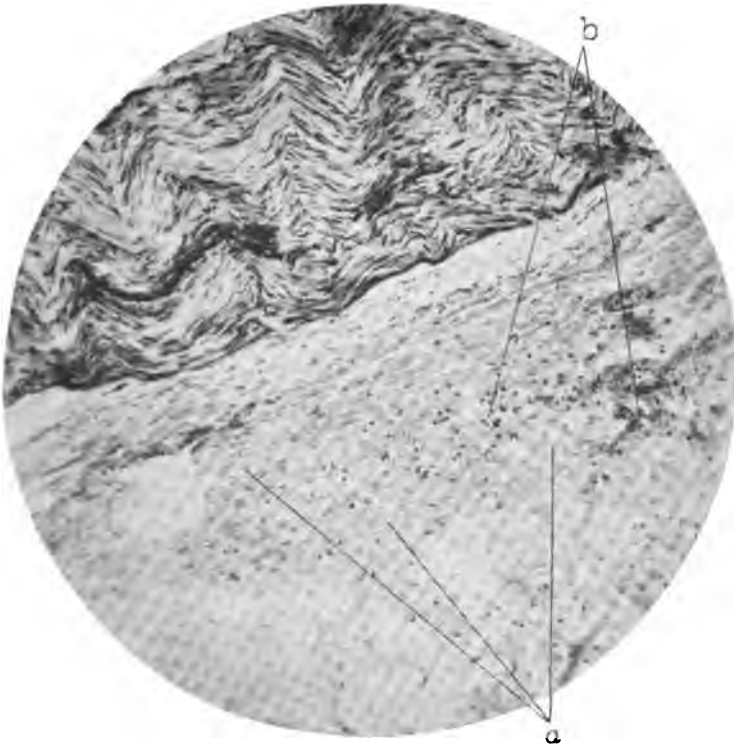


Fig. 256.—Hemorrhage (*a*) and leukocytic infiltration (*b*) in the sheath of the vagus just beyond the inferior vagus ganglion in Dog 225 showing visceral herpes seventy-two hours after an intravenous injection of the streptococcus from the tonsil in Case 278 ($\times 110$).

membrane following injection of these strains is in line with this idea.

The fact that visceral herpes with accompanying lesions of the vagus and sympathetic ganglia has been produced experimentally supports the view held by clinical observers that visceral herpes occurs in man, and since it occurred chiefly in animals with severe,

usually fatal, bilateral herpes, it affords experimental evidence in favor of the general impression that bilateral herpes is apt to end fatally.

The absence of streptococci in the clear blister-fluid, both in man and in animals, when the organisms present in the ganglia, and the presence of pain before peripheral lesions can be made out, suggest that the lesions in the ganglia are primary, and that the



Fig. 257.—Photomicrograph of a twenty-four-hour culture in ascites-dextrose broth of a streptococcus isolated from the spinal fluid in a rabbit showing herpes after intravenous injection of a streptococcus culture from the tonsil in a case of herpes zoster in man (281). The morphology is characteristic of other strains as well. Gram stain ($\times 1300$).

peripheral manifestations—herpes of the skin, the tongue, the lip, and the viscera—are secondary trophic effects. The occurrence of herpes in cases of pressure-paralysis of the spinal cord would seem to be in accord with this idea. But the finding of the streptococcus in the turbid, bloody blister-fluid in one case of our series in man, and in the severer peripheral lesions (skin, mucous membrane, tongue, and viscera) in experimental disease, the common occurrence of thrombosed blood-vessels, containing fibrin-

cocci in both the peripheral and central lesions, and the absence of bacteria and demonstrable changes in the intervening nerve-trunks, suggest strongly that while the primary milder lesions are trophic, making a "*locus minoris resistentiæ*," the severer lesions, presenting, as they do, all the features of an infectious process, are the result of a superimposed hematogenous infection.

It is a noteworthy fact that of the large number of animals injected with cultures from a variety of diseases²³ other than herpes in which lesions resembling those in man have been produced, none has exhibited typical herpes.

Since the streptococci lose the characteristic affinity after cultivation on artificial media, after animal passage, and apparently in the focus of infection after recovery, the conclusion seems warranted that the atrium of infection is not only the place of entrance, but the place where the streptococci, by growth in symbiosis with other bacteria, and under varying grades of oxygen-pressure, may acquire the peculiar properties necessary to infect in this particular manner.

It would appear then that herpes zoster is due to a streptococcus having elective affinity for the ganglia and the posterior roots. The possibility, however, that the disease in some instances may be due to other bacteria having a similar affinity must be admitted.

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VISCERAL CRISES IN ANGIONEUROTIC EDEMA *

EGERTON L. CRISPIN

A large number of the patients suffering from visceral crises, particularly of the erythemic, purpuric, angioneurotic group, are advised to have surgical operations, and many of them sooner or later submit to abdominal surgery, from which they do not obtain desired relief. I wish particularly to call attention to this group of cases and to discuss the diagnostic importance of visceral crises more from the standpoint of value in negating or avoiding surgery which does not give relief than from the standpoint of too closely differentiating interrelated medical conditions. I shall only mention visceral crises of syphilitic origin, for which surgery is occasionally done, and the abdominal pains of nephritis, particularly of the hemorrhagic type, to which Osler has called attention. Surgery is advised in these conditions only when examination has been incomplete.

The more or less widely varied manifestations of these affections with which are associated visceral pains have never been sharply differentiated, and are probably all members of the same group. It is probable that most of the allied conditions, as the urticarias, erythemas, and purpuras, have as an underlying condition an angioneurosis. Some of them may be caused by chemical irritation; others may be toxic in origin; and yet others may have resulted because of the nature of the individual and from faulty metabolism. It is probable too that anaphylaxis may be a basic cause of many of these angioneurotic conditions. In each of this

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entire group, localized vascular dilatation occurs and is associated with a serous or hemorrhagic exudation. Caspary¹ says the erythemas as well as the urticarias may result from the action of different toxins on the nerve-centers. Osler² suggested that the entire group of angioneuroses may depend on some poison which, in varying doses in different constitutions, excites in one urticaria, in another a peliosis rheumatica, and in a third a fatal form of purpura.

One of the conditions forming this group, a purpura with a more definite syndrome than many of the others, was described by Henoch.³ This condition is characterized by recurrent attacks of purpura and crises of abdominal pain, often accompanied by diarrhea and vomiting. Arthritis is present in the typical form of the disease. This type occurs most often in the young. Abdominal manifestations similar to those in Henoch's purpura, as Osler has shown, occur in erythema and urticaria. He also calls attention to the variability of the lesions of the skin and reports cases in which some of the attacks of agonizing colic have occurred with no cutaneous manifestations.

Some of the French writers have grouped both the purpuras and the urticarias under the erythemas. Wagner⁴ would have the exudative erythemas to include three forms at least: Erythema nodosum, erythema multiforme exudativum, and urticaria. Osler regards purpura rheumatica as the hemorrhagic type of an exudative erythema, and considers Henoch's purpura in the same group. In recording the variability of the lesions of the skin in these conditions, he shows that it is possible to diagnose at different times in the same patient simple purpura, simple urticaria, exudative erythema, arthritic purpura, and angioneurotic edema. Jacobi⁵ has shown the close affinity that exists between exudative erythema, Henoch's purpura, and angioneurotic edema. Advances in experimental medicine will in time separate such clinical grouping as Wagner has made. Within the past year Rosenow⁶ has experimentally produced erythema nodosum, and from his studies recorded a streptococcus as the etiologic agent in his experimental series.

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General attention was called to angioneurotic edema by Quincke's⁷ description in 1882. Since then a number of cases have been reported of the exudative erythemic state which indicates that the condition is fairly common. Graves⁸ described the condition in 1848, and Milton,⁹ in 1876, reported cases under the name of giant urticaria. Quincke's name for the condition is most generally used in this country and in England, though the literature abounds with synonyms. Most of the cases not showing purpura or joint affections are grouped under this head, though, as has frequently been noted, different attacks in the same patient may present a wide range of skin manifestations. Osler has called these varied skin manifestations angioneurotic dermatoses, noting that they are characterized by a marked disturbance of vascular tonus in addition to a more or less inflammatory condition of the skin, due to its abnormal tendency to react to slight and varied irritants, with resultant dilatation of the vessels and exudation. This sensitiveness of the skin and the abnormal reaction, the result of a general neurotic disturbance, must be distinguished from the action of inflammatory irritants.

All members of the erythema group may have visceral manifestations, or there may be visceral manifestations in the nature of crises associated with any or none of these varied angioneurotic external conditions. These visceral or gastro-intestinal crises may be so severe at first sight as to cause concern, and they may be without external clues in the nature of lesions of the skin. If the history is not carefully taken, the hurriedly called physician may easily be misled into thinking that the trouble must be due to the gall-bladder or appendix, or at least something that should be taken out. Because of the variability of the skin conditions or of their absence in some of the attacks, often patients do not associate the conditions and, unless they are carefully questioned, clues may not be obtained. Under visceral lesions of the erythema group Osler¹⁰ has reported 29 cases of these interesting conditions.

Of greatest diagnostic importance in these cases is the indefiniteness of the nature of the abdominal pain. The point most impressive in taking a history is that these pains, apparently

of great severity, do not conform to the types usually observed and known to be of a surgical nature. In children, particular care should be taken to get a full history, which may bring out the occurrence of previous attacks of lesions of the skin, inflammation of the joints, abdominal colic, or crises. In adults one is often struck with what is called a neurotic tendency of the patient. In questioning the patients who present themselves for examination and diagnosis between attacks, a wide oscillation will often be noted in their story and too strong a reaction to external stimuli. The crises of which they complain are described as being severe abdominal pain. One patient described her pain as "intense suffering"; another said that she had doubled up with the pain and rolled about on the floor. The abdominal pains come without food time relation, usually at any time. The nocturnal exacerbations are frequent. In one instance I observed a suggestion of regularity in the return of pain about the same time each night. There may be diarrhea, vomiting of blood, or there may be slight melena. The location of pain is usually midabdominal, or it may be general and described as "all over the abdomen." The usual radiations of lesions causing surgical conditions, however, are not found. Attacks in various individuals are usually of about the same duration—from six to eight hours. They vary in intensity from mild aching to such severity that it may be necessary to give morphin.

In cases in which attacks of pain are of a few hours' duration differentiation from disease of the gall-bladder, in which there is high epigastric location of pain, and the sudden onset and cessation of pain in some of the attacks, are diagnostic; in renal colic the radiation, localization, urinary findings, cystoscopic and roentgenologic findings may be used to clear up differential conditions. In obstructions of the intestine, the prolonged condition in single or few attacks and the causes for obstruction with the general symptoms should prevent confusion. It should be borne in mind that visceral crises of the types under discussion are caused by the results of vasomotor changes and that, with the onset, sufficient time must elapse for exudation to reach the painful stage and likewise for its disappearance. There is more constancy in time of

onset, duration of pain, and in the way pain disappears in different attacks than in the various surgical conditions with which these crises may be confused. Disease of the gall-bladder probably is most often confused with the attack of a few hours' duration, though peptic ulcer is sometimes confused with it, particularly when vasomotor conditions have occurred in the stomach and permitted sanguineous seepage. It is then the cases of few hours' duration that must be differentiated from upper abdominal surgical conditions.

There is another type probably resulting from the same primary cause that is occasionally mistaken for appendicitis or appendiceal abscess in which the onset and disappearance of pain are more gradual. A swelling often appears in the lower right abdomen, which suggests appendiceal abscess. There may be increased temperature; the symptoms, usually of comparatively short duration, are out of proportion to the patient's general condition, which is fairly good. In operating on these patients a brawny induration, often of the whole cecum and appendix, thick walled and somewhat hard, is found. Occasionally the big gut above the cecum is involved for several inches. The appendix does not show sufficient changes to be the primary cause of the condition. One of the most striking features is the rapidity with which the patients recover. A day or so after operation they are well except for such discomfort as may be present from the abdominal incision. Further inquiry into the history may disclose the presence of swellings in the skin at various times. In the exudative types of longer duration more of the cecum seems to be involved than other parts of the viscera, partly because the frequency of appendicitis and the presence of tumefaction permit more frequent exploration.

Often attacks of abdominal pain occur which last for some time with no other suggestive diagnostic clues; but in some of these cases inquiry brings out a history of hives, swellings (hard, white, burning) in the skin, purpura, puffing of face, eyelids, cheeks, cold hands and feet, etc.; also swelling in the throat causing dyspnea and danger of suffocation. Attacks of transient bronchorrhea occurred in one of the cases observed. This bronchorrhea should always be

looked for. That there is swelling in the viscera analogous to that in the skin has been quite definitely proved. It is believed that the exudation of serum and distention of the visceral coats produce pain and, when sufficient to cause pseudo-obstruction in the intestines, the pain is peristaltic. When there is great distention of the visceral wall, there may be severe pain and considerable exudation of blood into the stomach, which may be vomited. In these cases a diagnosis of ulcer is sometimes made. Morris,¹¹ when giving a lavage at the beginning of an attack, brought out a piece of gastric mucosa thickened with a simple, non-inflammatory edema. Harrington,¹² when operating during an attack of colic, found an urticarial swelling of the gastro-intestinal wall. Lennander¹³ says that either serous or hemorrhagic infiltration of the wall of the stomach or intestine, if sufficient to produce stretching of the parietal (mesenteric) attachment, will produce colic. Osler¹⁴ cites three cases in which laparotomy was done without definite findings. He quotes cases of Sutherland and Burrows confirming the view that colic may be due to infiltration of the intestinal wall with blood and serum. Some of the indurative, edematous conditions occasionally found at the operating table in which histories have not been definite undoubtedly are of this type, and surgery is of doubtful benefit. Riggs¹⁵ cites four cases of thickening of the ileum and cecum that he regards as visceral manifestations of the condition, having for its outward signs erythema, angioneurotic edema, etc. Three cases of induration of the cecum and adjacent gut have been observed in the operating room by W. J. Mayo.¹⁶ Before operation, because of the tumefaction, these cases had suggested appendiceal abscess. The induration was found in the cecum and in the appendix without sufficient cause. These patients got well with striking rapidity. A history of swelling of the skin was obtained afterward.

Patients in the angioneurotic group with visceral crises have repeated attacks, sometimes for years, that cause great discomfort. No deaths have been reported from visceral causes in this condition, though some have been reported from edema of the larynx by Morris¹⁷ and Griffith.¹⁸ Often patients coming under ob-

servation have had surgical operations and, more often, have had them advised. It must be borne in mind that even with a severe angioneurosis there may also be true pathologic conditions in the abdomen which should be treated surgically and which operation will verify. However, in the group of visceral crises under discussion there seemed to be no permanent visceral lesion for which surgery could give relief. A history carefully taken and considered, particular inquiry in regard to lesions of the skin such as have been mentioned, inquiries as to transient bronchorrhea (Halstead¹⁹ gives extensive literature of the laryngeal group), sources of exogenous and endogenous poisons, particularly reflex sources that may be bases for anaphylaxis, and a more thorough physical examination will often help clear up a diagnosis from a surgical-medical standpoint.

In cases seen for the first time in which there is large tumefaction of recent duration in the cecal region, severe pain without local peritonitis, and with the patient in good general condition out of all proportion to the suspected lesion, a history of swelling should be carefully sought, and, if found, watchful waiting is good surgery. The cases cited here emphasize the necessity for careful differentiation of factors that may be brought out in the history which should help make a definite diagnosis.

Of the entire group of exudative erythemas, 50 were diagnosed angioneurotic edema. Abstracts of illustrative cases are appended.

CASE 137,701.—L. M. Unmarried woman, aged sixty years. Examined August 14, 1915. This patient complained of chronic constipation and hives. The constipation had existed many years; the hives began eighteen months before, and had appeared every night for some months. She had swelling over her entire body, lasting five or six hours, then gradually fading away. At times her head and face swelled so she could hardly see; her lips were swollen and protruded. The swelling was sometimes accompanied by hives, which were raised red blotches sometimes covering the entire body. The itching was almost unbearable. She complained of "intense suffering in abdomen"; no localization, but all through the abdomen, which lasted a few hours and then subsided. She had been told that she had appendicitis or

peritonitis, and that the large bowel was contracted to the size of a lead-pencil. She was neurotic; her brother said they never crossed her because of her nerves. She was well nourished, had gained weight the last year.

Physical Examination.—Gastric analysis practically normal. Roentgen examination of the bowels showed no abnormality other than incompetent ileocecal valve. At one observation there was a raised red, circumscribed area, irregular in outline and the size of a half-dollar, in the posterior left lumbar region. This was a type of the hives that came out profusely each night. The adjunctive special examinations gave no added information as to the cause for her condition. A diagnosis of angioneurotic edema with visceral manifestations and colonic urticaria was recorded.

CASE 133,719.—T. M. S. Married woman, aged thirty-seven years. Examined June 21, 1915. This patient complained of recurrent cramps in the upper abdomen with loss of strength. For many years she had been easily exhausted. For the last four years she had had frequent cramps in the abdomen lasting from one to four hours. The attacks were of gradual onset, came irregularly, and could not be relieved. After the pain was over there was soreness; no relation to food; no radiation. She would lie on the floor and double up when the cramps came on. With the severe pain in the abdomen she was sometimes nauseated, but never vomited. For four years there had been swelling coming at any time over body, face, and extremities, sometimes about joints. Her face had been so swollen as to have been hardly recognizable. The swelling sometimes lasted from one to three days; itched and stung; it was often circumscribed. The patient was very sympathetic, did everything with great zeal, feeling joy, sorrow, etc., with intensity. She did not associate the lesion of the skin with the abdominal condition and it was brought out only by questioning.

Physical Examination.—The right side of the patient's face was greatly swollen; this was painless, though it felt stiff to the patient. Examination of intestinal tract clinically and with the roentgen ray did not reveal anything of value. Many adjunctive examinations made for record and completeness gave no further information. A diagnosis of angioneurotic edema with visceral crises was made. The patient came to the clinic expecting to have an operation on the gall-bladder.

CASE 101,588.—W. H. S. Man, aged forty years. Paperhanger. Examination March 4, 1914. This patient had been

urged a number of times to have operations for gastric ulcer. He had had gastric trouble off and on for twenty-three years. When seventeen, he had had cramps so severe as to double him up. He used to tie a towel tight around his waist and a number of times was rolled over a barrel to relieve the cramping pains. These attacks came frequently for a few weeks, then disappeared for weeks or months. Only occasional trouble between the ages of twenty and thirty. When about thirty-one he had an attack and vomited a large handful of clots of blood. Sometimes the pain came while eating, at other times when he was hungry; apparently no clear-cut food relation. Nothing relieved the pain. Small clots were vomited again about two years later. For three years prior to examination there had been a series of attacks—about one a year. Present attack had lasted about three weeks. No regularity; stomach better midway between meals. For three months he had noticed great blotchy swellings come out on his skin. Swellings usually came about eight in the evening and lasted until about one in the morning. Skin became thick and hard, and stung. At times the skin at the joints was so thickened that the normal use of the joint was impossible. Slight swelling on the face, but swellings on the back and thigh areas as large and thick as a man's hand appeared in a few minutes and were gone the next day, leaving only a little tenderness in the skin. He gave a history of profuse expectoration at times, spitting a quart or more in an hour or two and coughing up large quantities of watery mucus so that it would run out of his mouth. While under observation the patient lost eight pounds within four days. He had no pain during this time, but disturbances of the skin were marked each night. He said he sometimes lost 40 pounds in two months while having this trouble, but soon gained it back. Appetite good while losing weight.

Physical Examination.—Roentgenograms showed considerable fibrosis of the lungs and a lesion of the stomach at or near the pylorus. After this examination of the stomach and while still in the dressing-room, the swellings were observed coming out. Within ten minutes thick, raised, hardened areas the size of half a dollar were noted on the thigh. Further examination revealed areas nearly as large as the palm of the hand over his back. Though the angioneurotic condition was recognized, because of the history of hematemesis and roentgen findings exploration was advised. At the operation nothing was found in the stomach. The gall-bladder was removed, but, when opened, revealed doubt-

ful pathology. An obliterated appendix was also removed. One year later the symptoms were the same as before operation without noticeable change in any characteristics. The lesion at or near the pylorus reported by the roentgenologist was probably a visceral swelling. Seventeen months later the patient's physician reported attacks of abdominal pain and skin manifestations, the same as before. The last attack of pain was of the usual type, being in mid-epigastrium, severe, lasting from seven in the evening until half past one, during which time the patient was given one-half grain of morphin. Swollen areas in the skin were large and numerous. It is interesting to note that a little alcohol will always precipitate these attacks of angioneurotic edema and crises.

CASE 177,381.—A. J., man, aged twenty-nine years. This patient first came to the clinic December 16, 1912. Bronchitis and asthma were diagnosed. Nasal polyps were removed and the antra irrigated. He returned February 17, 1913, feeling much better. On July 2, 1914, he again returned, complaining of attacks of abdominal pain coming on soon after meals and causing much discomfort. Repeated examinations did not reveal the nature of this pain, and the patient was referred to the hospital, where he remained forty days. Severe pains in the epigastrium at 10 P. M. lasted three hours and required morphin. During this time spells of angioneurotic edema were recorded, varied in distribution, and lasted from a few minutes to a day. Purpuric hemorrhages were noted a number of times. Coagulation time of two minutes was recorded. The abdominal pains persisted usually during the night. No relation to meals. There was an eosinophilia for which no cause was found. Though the angioneurotic edema and purpura had caused the patient to be under observation for weeks and the nature of the pains was believed possibly due to the same cause, yet some features of the patient's illness made exploration advisable, and August 26, 1914, a cholecystectomy was done for enlarged gall-bladder, "showing an indefinite cholecystitis." The appendix, which was ruptured at the tip and sealed by the small intestine, was removed. The pancreas was apparently normal. Three months later his home physician stated that the symptoms continued, differing in no way from those before operation.

CASE 76,027.—W. T., man, aged thirty-nine. Examined November 13, 1912. About ten days before admission to the clinic the patient had had an attack of general cramping abdom-

inal pain. Soreness became localized in the right lower abdomen. Three years before he had had a similar attack accompanied by blue-black spots thought to be acetanilid poisoning. In November, 1914, another attack of pain occurred to the right of the navel, with severe vomiting, gas distress, and marked tenderness in right iliac fossa. Operation November 14, 1915. On opening the abdomen a quantity of free fluid without flakes of lymph and without odor came out. The coil of the ileum 14 inches in length 2.5 feet from cecum was thickened, purplish red, and distended. The intestine above and below was normal. Peritoneum shiny; no evidence of necrosis. Intestinal wall greatly diminished in lumen by reason of thickening. There was a subacute condition of the appendix, which evidently was the cause of the attack ten days ago. The appendix was removed. A diagnosis of angioneurotic edema was recorded.

CONCLUSIONS

1. Severe abdominal pains which do not conform to the true surgical types may be confused with visceral crises for which surgery would be of no benefit.

2. When a history of severe abdominal pain is given which does not conform to true surgical types, careful inquiry should be made as to the presence at any time of urticarias, erythemas, purpuras, and swellings of angioneurotic edema types.

3. A history of recurrent severe abdominal pains with constancy in the nature and duration of the attacks with skin manifestations of any of the exudative erythemic forms, with or without noticeable association with the abdominal pains, should excite suspicion as to the presence of crises of angioneurotic type.

4. A diagnosis of visceral crises of angioneurotic type should not be made until careful examination has excluded or made independent surgical causes. In this, roentgenologic examination of the gastro-intestinal tract is valuable negative evidence. Syphilis and tuberculosis should be excluded.

5. The constancy in the recurring attacks of pain not conforming to surgical types in patients who have had skin manifestations of the exudative erythema group and whose general condition does not account for the suffering they have had to bear will warrant a diagnosis of visceral angioneurotic edema.

6. Repeated or even single attacks of intestinal colic with tumefaction in which the patient's general condition is too good for the extent and severity of the trouble and in which history of swellings can be obtained, may be of this type. The rapid return to health is strongly suggestive of visceral angioneurosis.

7. Having determined the medical nature of these angioneurotic visceral crises, or even in these cases of angioneurotic edema or the entire exudative erythema group, we should endeavor to work out the sources of toxemia. These may be: Foci of pus in the upper respiratory tract and sinuses, bacterial absorption, idiosyncrasies to heat, cold, chemicals, parasites, carbohydrates, or proteins that are the causes for anaphylaxis.

8. Removing the causes for anaphylaxis, whether it be an idiosyncrasy in the patient for ice-cream, foreign protein, banana, alcohol, or any anaphylactic base or source of exogenous or endogenous irritation or poison, may give the patient relief that the advised surgery would not have given him.

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OBSERVATIONS ON THE CLINICAL PROGNOSIS OF SYPHILIS *

GILBERT J. THOMAS

The discovery of the spirochete as the causative organism in lues, the Wassermann reaction, and salvarsan have given to the medical profession definite diagnostic aids and a "near" specific in syphilis.

Physicians who thoroughly examine their patients and who take advantage of laboratory tests see more cases of syphilis in various stages than have been heretofore observed. This is not because of a greater prevalence of the infection, but because of the greater aid afforded by the isolation of spirochetes, and because by means of the serologic tests we are now much better able to diagnose lues.

The Wassermann Test.—Much has been written about the unreliability of the Wassermann test. In our experience in the Mayo Clinic there is less than 1 per cent of error in the positive findings; and treatment has corroborated these findings. There have been a few false positives in cases of cancer, tuberculosis, scarlet fever, and Hodgkin's disease. Between 25 and 30 per cent. of the patients who complained of lues have given a negative Wassermann. These cases were mostly tertiary and so-called parasyphilitics. A provocative dose of salvarsan or neosalvarsan, or the use of mercurial inunction for the same purpose, has been a very great aid in the Wassermann technic. Many cases shown to be negative return strongly positive after the administration of anti-specific drugs in provocative dosage. This is especially true of tertiary lues.

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The Wassermann test is valuable also in that it indicates the drug best suited to the patient under consideration. In some instances I have found neosalvarsan effective when salvarsan would not reduce the strength of the reaction; and in some cases that mercury in large doses would reduce the Wassermann reaction after salvarsan had failed. After the institution of treatment the negative Wassermann test should never be used as an indicator of sterilization, but as a sign that the particular drug employed is destroying the spirochete, either directly or by the formation of antibodies.

In a number of cases of secondary lues I have noted that the spinal Wassermann is positive, indicating that early invasion of the central nervous system may occur and not show symptoms for a number of years. For this reason the spinal Wassermann should always be used in secondary cases; and the spinal test should be made frequently during the course of treatment. In the tertiary syphilitics, and in the so-called parasyphilitic cases, or in suspected cases without history and without definite findings, the spinal Wassermann should be a routine procedure. In a number of suspicious but atypical cases a positive spinal reaction was the only confirmatory finding. This has been especially true in a number of old syphilitics with no clinical evidence of lesion in the central nervous system.

Diagnosis.—In the diagnosis and treatment of lues it should be remembered that this is more than a skin and venereal affection: it is a constitutional disease which may attack any organ or tissue. We do not find as many surface manifestations of the disease as in the past; and, when found, they are not prominent. Comparatively few primary and secondary luetics are seen in the Mayo Clinic. A great many visceral and central nervous lesions and a great many parasyphilitics are seen. The diagnosis of the primary lesion is positive in every case of untreated chancre. The finding of the spirochete is not difficult, and may be accomplished by any physician who has a microscope and some India ink.

The fact that about 20 per cent. of the primary lesions of lues are extragenital should seriously concern us as physicians. A large

number of physicians and surgeons have their fingers and hands infected; and we see many primary sores about the mouth, eyes, nose, and throat. Any slow-healing lesion, genital or extragenital, whether or not it shows induration, should be considered luetic, and serum should be examined for the spirochete; if found negative, the patient should be watched for the approach of secondary invasion. A great number of patients come to our clinic every year for chronic nose, throat, and mouth conditions which prove to be lues. Many undiagnosed conditions of the eye are found to be luetic when examined by a specialist and checked up with a Wassermann test. In our experience a complete physical examination, including expert tests of the special sense-organs in combination with the roentgen ray and the Wassermann, show a correlation of findings which makes the diagnosis comparatively easy. A carefully taken history, with consideration of the patient's ancestors and immediate family, will sometimes reveal a basis for the suspicion of a luetic taint. Most patients are truthful when giving their history to the physician, and state only the things which, in their judgment, are important. In my experience a history of infection long forgotten is frequently elicited when the patient is informed of the suspicion, and allowed time to review his past complaints. For example: a patient came recently with a fair history of gall-bladder trouble of long standing, but the attacks were atypical and the man's appearance suggested some constitutional disease. He gave a negative history of infection, and was considered a surgical case. The examining physician noted that there had been no children and no pregnancies in his family, and advised a Wassermann test, which was strongly positive. When the patient was presented with the result of the serologic test, he denied infection; and the test was repeated and again found positive. The ways in which the disease might be contracted were explained to the patient; and he was advised to think over his previous illnesses, and report the following day, which he did to the effect that while working in a dissecting-room (he had studied medicine for two years) he had cut his finger. A sore developed which did not heal for some months. This story may or may not have been true, but,

without cross-examining, and by informing the patient that the serologic test might be in error, the history of probable infection was obtained.

The preponderance of tertiary, nervous, and parasyphilitic cases over the number of primary and secondary infections does not speak well for the permanence of the treatment which has been instituted within the last ten years. I believe that many of these patients have been insufficiently treated even since the discovery of salvarsan. In a few years after being pronounced cured, they develop incurable lesions of the blood-vessels, viscera, or nerves. In many instances the usual course of the luetic infection is interfered with by the removal of the primary growth and the institution of inadequate treatment for too short a period. This explains why so many luetics of this type escape diagnosis until their entire history is taken and complete examination made. The examinations in the nose, throat, and eye departments frequently enable us to make diagnosis in cases with obscure histories and clinical findings. In a number of patients complaining of urinary difficulty, a thorough cystoscopic examination revealing a typical cord-lesion of the bladder has given the first hint of the cause of the trouble. In a number of ways the roentgen ray has led us to suspect lues, especially by showing shadows in the chest due to tumors, glands in the mediastinum, and enlargements of the heart and greater vessels. The roentgen ray has helped in the diagnosis of the condition of bones and joints. The roentgenogram has also cleared up a number of obscure gastric conditions by showing contractures and other signs indicating the possibility of lues.

In making routine Wassermann tests I have been impressed with the great number of positive reactions on all patients showing heart-lesions and those with clinical findings of heart or blood-vessel pathology. One observer has stated that there are few luetics who do not show, during the first five years of infection, blood-vessel changes beyond their years. Also, he states that congenital luetics very frequently show marked blood-vessel changes before the tenth year of life. In our experience most of the heart-lesions which are not preceded by a definite history of rheumatic or ton-

sillar infection have been due to lues, and all cases should be looked upon with suspicion. The roentgen ray is indispensable in making a diagnosis of enlargements of the vessels and the heart. Several of our cases of mediastinal tumors revealed by the roentgenogram have proved luetic, both serologically and by treatment. The examination of the luetic should always include a good roentgenogram of the chest showing the heart and the large vessels. In this way the diagnosis has been cleared up in a great many patients who complained of pain located between the shoulderblades and thought to be due to gall-bladder trouble. Another group of patients, with luetic histories, complaining of high abdominal pain consequent to luetic enlargement of the heart or aorta, have been observed in the Mayo Clinic.

A surprisingly large number of gastric conditions have been proved luetic in origin. The roentgen ray and screen examination have contributed largely to the diagnosis of these cases.

Syphilis of the liver has been a somewhat frequent finding, especially in those cases showing enlargement of the left lobe. In a high percentage of cases the spleen is found enlarged. There has been no typical history or findings in these cases except the frequent enlargement of the left lobe of the liver. Every patient with enlargement of the liver should have a Wassermann test; and, if the diagnosis cannot be otherwise explained, a provocative drug should be given and the Wassermann test repeated. If surgery is not urgent, or if the case is medical, antisyphilitic treatment should be tried.

In a number of cases proctoscopic examinations for rectal complaints have disclosed typical contractures, which have been the only findings suggestive of syphilis. The introduction of the proctoscope should always be practised in patients complaining of rectal trouble. In a few cases the diagnosis of syphilis has been suggested by the laxity of the rectal sphincter found on digital examination.

Treatment.—It has been the opinion in our clinic that salvarsan properly administered for a sufficiently long period will probably cure lues. After recovering from their symptoms, patients frequently stop treatment; therefore the necessity of the continuation

of some kind of treatment for at least three years should be impressed upon them. In some instances patients remain under observation only long enough to receive several injections of salvarsan. To supplement this they must take treatment, either salvarsan or mercury, for at least three years, when they may be encouraged to expect cure, though they should not be assured of it as a certainty. I agree with Ormsby in his statement that it will be fifteen years before we can have proof of the permanence of cures effected by our present methods of treatment. Physicians treating patients with salvarsan or other specific drugs should keep a very careful record of the drugs used, total amounts given, methods of administration, intervals between treatments, and the length of time the patient is under observation. In this way only can an outline for uniform treatment be formulated which will indicate the best drug or combination of drugs to use in the different stages of lues, and will afford a complete record of a large number of cases so that the permanence of our cures can be correctly estimated.

Intravenously, I employ either salvarsan or neosalvarsan. The new drug can be given in larger quantity and more frequently than salvarsan. It is easy to prepare, and should be the one chosen. The first requisite in intravenous medication is *pure* water. This can be obtained only by distillation and thorough sterilization. The water should be used the same day it is distilled; but if it has not been opened, resterilization is sufficient for its use on the following day. If, after this preparation, one cannot be sure of the water, a control injection should be given of water alone in the same amount that would be required for the salvarsan solution. This insures any reaction following salvarsan medication to be due to the salvarsan and not to the water. A large amount of apparatus is not necessary for intravenous medication, even when using salvarsan. A 25 c.c. syringe, one and one-half inches of rubber tubing of small caliber, and a needle of moderate caliber are all that is necessary.

The preparation of the drugs is important, and should be carefully carried out. A complete solution should be made of either salvarsan or neosalvarsan before it is used. All the precautions

found on the wrapper of every ampulla should be carefully read at least once before a patient is treated. If these precautions are taken, complications can be averted, and salvarsan becomes practically a harmless drug.

Of special importance are the solubility and the alkalization of salvarsan. The drug should be put into very hot water, and enough sodium hydroxid should be added to get a clear amber solution. After this has taken place several drops of sodium hydroxid should be added to make doubly sure the solution is distinctly alkaline. I have never seen any bad results from overalkalinization; on the other hand, deaths have been reported from using the acid solution. The operator should be extremely careful that the drug is well dissolved in the hot water before introducing the sodium hydroxid. When using a syringe and concentrated solutions, the addition of salt solution is not necessary. I have seen less reaction when using salvarsan in a concentrated solution in water only when thoroughly alkaline than when using the old method of dissolving the mixture to 300 c.c. with salt solution. As I have stated, salvarsan in from 0.2 to 0.4 gm. doses in concentrated solutions is now being used in our Clinic. If this mixture is injected very slowly and is thoroughly in solution, there is no more reaction than in using the diluted method. It is not necessary to incise the arm nor to dissect the vein. With a little care and practice a needle can be introduced directly into the vein. If a needle of fair size is used, clotting is not frequent. A free flow of blood indicates to the operator that the needle is within the lumen of the vein, and injection may begin. The patient should be supine, with the arm extended at right angles to the body and lying loosely on a small board, which can be attached to the table.

In a few primary cases I have observed salvarsan has been given in small doses twice a week for three or four doses, and then in larger doses until eight to ten injections have been given. The reaction of the patient, and the character of the urine, should be the guide to increased dosage and to frequency of administration. The sore can be treated locally by thorough cautery, surgical removal, or by the application of antispecific drugs. I have found

an emulsion of salvarsan one of the best dressings that can be applied to chancre. The patient is advised to return from four to six weeks after the disappearance of his chancre, at which time a Wassermann is taken before and after provocative medication. He is also advised to return for examination and for serologic tests every three months the first year, and every six months for the following two years. During one of his subsequent visits a spinal puncture and Wassermann on the spinal fluid should be made.

In secondary cases the dosage should be smaller and cautiously administered, since the reactions from dead organisms are frequently observed and have been known to cause the death of the patient. Mucous patches may be treated with salvarsan emulsion in connection with the intravenous medication. These cases are treated twice a week as long as they have a reaction, and then every other day until the Wassermann is negative. If they are symptomless at this time, mercury medication is advised after a rest of one or two weeks. The mercury is to be taken by inunction or by intramuscular injection in large quantities for six weeks. The patient is then advised to rest again for a short period. In this group of cases the Wassermann should be frequently taken, not as an indicator of sterilization, but to show the progress made in the treatment of the patient. We found in some cases that the Wassermann remained positive despite salvarsan medication, but that neosalvarsan or mercury quickly changed the reaction.

Eye complications or lesions of luetic origin have not been found a contraindication to arsenic therapy. When the destruction was not complete, a great many eye conditions have improved. In our earlier work the eyes were routinely examined before the first dose of salvarsan was given; at the present time complications in the ears are more especially investigated.

In treating many cases of aneurysm and valvular disease of the heart a very marked improvement symptomatically and a slow but steady decrease in the size of the roentgen shadow have been noted. Many valvular lesions without pathology in the large arteries have been permanently and completely relieved by salvarsan. I had one very interesting case of complete heart block,

which was permanently relieved after three intravenous injections of neosalvarsan. No difficulty has been experienced in treating the largest aneurysm when small doses and concentrated solutions were used, thus not affecting the blood-pressure. It is our practice in these cases to precede the arsenic therapy by large doses of mercury. The mercurial treatment tends to reduce the amount of reaction occurring in most cases after the first and second injections. Enlarged glands within the mediastinum respond quickly to treatment.

Syphilitic infection of the stomach is a frequent finding, and it seems to be a very favorable condition for treatment. I have collected between 20 and 30 cases which, by the history, roentgen ray, serologic findings, and treatment have been proved to be gastric lues. Such patients are quickly relieved of their symptoms. Their gain in weight and constitutional improvement are very marked. The roentgen ray is a great aid in making the diagnosis and in ascertaining the degree of improvement after treatment. A few patients in this group failed to improve under treatment; they showed ulcer at operation. This brings out a point that should always be remembered—that syphilitic patients may have lesions not dependent on the syphilitic invasion, and that tissues or organs thus affected may give rise to symptoms recognized as independent of the luetic infection.

Gumma of the liver and spleen is not so quickly relieved as luetic tumor located elsewhere in the body. By persisting with treatment I have seen a very large gumma of the liver gradually reduced in size. A case of this kind requires persistent and continuous treatment, either arsenic or mercury and iodid in large doses. Bone and joint conditions show early improvement, but cures are very slow, and this type of case seems to respond more quickly to combined mercury and arsenic treatment than to either given alone. I have not had a great deal of experience with the intradural method of treatment in lues of the nervous system. I have, however, made several intradural injections, using arsenized serum and minute dosage of neosalvarsan in solution, but the results from this mode of treatment do not seem to be more permanent or more

marked than when the treatment is carried on intravenously. Such cases should have repeated small injections two to four times per week. Very marked improvement in the symptoms, and especially in the general condition, of these unfortunate individuals has been noted. In a few cases there has been a reversal of the spinal Wassermann after intravenous medication or the combined arsenic-mercury treatment. All these patients should first have intravenous treatment, and intraspinal treatment if the first is not sufficient to relieve symptoms. Our aim is: (1) To improve the general tone of the patient; (2) to arrest the progress of the disease; (3) to improve the symptoms complained of; (4) to bring about a general symptomatic and serologic improvement; and (5) to cure.

CONCLUSIONS

The discovery of the spirochete, the Wassermann reaction, and salvarsan are efficient means for the diagnosis and proper treatment of syphilis. The permanence of our cures cannot be estimated until a sufficient time has elapsed for the assembling of complete and thorough record—showing the drug employed, amount used, method and manner of administration, serologic and symptomatic improvement, and cure. Syphilographers in particular, and the medical profession in general, should advise their patients to see their physicians frequently regardless of whether or not they have symptoms of recurrence, in order that thorough serologic and clinical examinations may be made. The diagnosis of blood-vessel, visceral, and nervous lues is frequently missed because complete physical examination is not made, and because the correct interpretation of serologic and other tests becomes more difficult as the disease progresses. The complete examination of the special sense organs, and the use of the roentgen ray, should always be employed, as these findings are indispensable. Every luetic patient should be thoroughly treated; the longer the history, the more prolonged the treatment should be. Some degree of improvement is noticed in every thoroughly treated luetic patient.

CLINICAL OBSERVATIONS ON LUETIC DISEASE OF THE HEART AND AORTA *

ROBERT D. MUSSEY

Luetic disease of the heart and aorta has been brought into prominence within the last five years by the Wassermann test in conjunction with the radiographic and fluoroscopic findings.

I shall not attempt to discuss the abundance of valuable literature on this subject, but shall merely recount some of the observations made on patients as they have presented themselves at the Mayo Clinic: (1) As to their principal symptoms; (2) as to the most commonly found and pronounced physical findings; and (3) as to the results obtained by treatment. No effort has been made to follow out the experimental or pathologic aspects of the conditions.

Of 1379 patients with syphilis examined during the five years ending January 1, 1915, there were 59 with diseases of the heart, aorta, and mediastinum which were attributed to the specific disease, and 14 in whom cardiac lesions were noticeable, but of secondary importance. Only cases in which a definite diagnosis could be made are included in this report, and a number have been discarded because the history and findings were not sufficiently clear-cut for the purpose of tabulation. A large number of very early cases in this way are possibly not included.

In 53 of the 59 cases there were positive Wassermann reactions, a majority with total inhibition; and in the remaining 6 there were positive histories of syphilis. In connection with this incidence it is of interest that many of the patients as they presented themselves

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were past the secondary stage. Other infections may have played a part, yet only 4 patients had had scarlet fever, 4 typhoid fever, 3 chronic and 2 acute rheumatism, and 2 gave a history of attacks of tonsillitis. Fifty of the patients were men, and 9 were women. The oldest was sixty-seven, the youngest twenty-seven; and the average age was forty-seven years.

For the purpose of contrast, the cases have been divided into three groups. It was found that the syndrome and the physical findings of these three groups were rather sharply drawn; and since it seemed that a comparison of them in each group might be of diagnostic value, a tabulation has been made.

GROUP I.—CARDIAC AND MEDIASTINAL, 16 CASES—SYMPTOMS

Of this group 15 patients complained chiefly of dyspnea, 5 needing extra pillows when reclining. The same number complained of pain, which was described as dull, sore, sticking or catchy, usually in the chest, but in two cases it was noted in the abdomen. Other of the prominent symptoms were dizziness, congestion of the face, and gastric disorders. In 3 there was a history of edema. The longest duration of symptoms was twelve years, the shortest, two months; average, twenty-one months.

GROUP II.—AORTITIS, 18 CASES—SYMPTOMS

No special symptoms were prominent in this group. Pain, dyspnea, cardiac and gastric disorders, and weakness were most frequently mentioned. One patient complained of gas, 1 of urinary trouble, and 1 of staggering. Pain was noted in 12 cases; a history of edema in 3. Two patients were so dyspneic as to be unable to lie flat. The longest duration of symptoms was six years, the shortest two months; average, two and one-half years. In 11 cases the illness was constant; in 9, worse at times.

GROUP III.—ANEURYSM, 25 CASES—SYMPTOMS

Pain was noted as the predominant complaint in 15 of these patients, and was present in all but 1. It was mostly precordial in 14 patients; down the left or right arm in others; to the back in 18,

being described as dull, severe, progressive, or griping; taking the breath in 1, nocturnal in 3, anginal in 1. Among other symptoms were abdominal disturbance in 2; swelling (aneurysmal mass) in 6; cough in 4; pressure, weakness, or dyspnea alone in 3. Three patients gave a history of edema. Four needed pillows, 2 because of pain and 2 because of dyspnea. The longest duration of symptoms was twelve years, the shortest, three months; average, six years and eight months. In 23 of the 25 the complaint was constant, in 11 worse in spells.

General Symptomatology in the Series.—In 24 of the total 59 cases comprising the series, pain was increased by exertion. In the cardiac and aortitis groups the incidence of gastric trouble is of interest, occurring 11 times in each 16 and 18 cases, while only seven times in the group of aneurysms (25 cases). In 24 the food-intake increased the complaint. A history of gas, pressure, and epigastric pain may be of great value in the differential diagnosis of this group of cases from upper abdominal lesions, especially of gall-bladder disease.

It must be remembered that there may be coincident aortic and abdominal trouble. This was manifested in our series by one of the patients who later had a resection of the pyloric end of the stomach for ulcer. The chief complaint may be misleading, and the diagnosis may be missed without a careful history and examination. Examples of such misleading symptoms are chills, malaise, dizziness, "staggering and paralysis," nervousness and burning, and frequent urination.

In this entire series it may be noted that the majority of the patients were ambulatory. Those of the cardiac group showed most disability, and those of the aneurysmal least. (Six in the first group, 2 in the second, and 1 in the third had edema at the time of examination.) Dyspnea and edema in the cardiac, dyspnea in the aortitis and pain in the aneurysmal group were the greatest symptomatic factors in the production of the disability.

Group I.—Cardiac and Mediastinal.—Physical Findings.—The prominent findings in this group were irregularity of the pulse and a tendency to tachycardia, the average rate being 98. In only 2

was the pulse noted as normal. Six had edema at the time of examination. Venous pulsation in the neck occurred in 4 cases. Valvular murmurs were found in all but 6, the predominant being a systolic at the apex, with a systolic murmur at aortic area next in frequency. Cardiac dulness was normal in 4 cases, in 1 of which it was due to pulmonary emphysema; increased to the left in 10, and markedly so (a three-inch or more dilatation and hypertrophy) in 7, and to the right, also, in 6 more. A broadening of the mediastinal dulness was found in 3 only. Radiographs which were taken in 7 of the 11 cardiac cases showed cardiac enlargement, and in 2 of these a mediastinal shadow. The two had predominant cardiac symptoms. In all 5 mediastinal cases a well-defined shadow was shown. Irregularity of the pulse, broadening of the cardiac or mediastinal dulness, and the radiographic evidence were the most important findings in this group.

It is of interest to note that in the majority of cardiac cases there was evidence of nephritis, in most instances of rather severe grade, and that this was not true in the other groups.

Group II.—Aortitis.—Physical Findings.—In this group irregularity of pulse was observed once only, while the water-hammer was noted 7 times in the 18 cases. The average pulse-rate was 87. A thrill over the aortic area or carotid was noted in 7 cases. In all but one of these there was definite evidence of cardiac hypertrophy to the left, in 14 not over a two-inch increase. Increase of the right occurred in 7, and a broadened aortic dulness in 8. The radiogram showed the heart enlarged in 14 cases and the aorta in 7. The relative cardiac enlargement was less marked than in purely the cardiac cases. A to-and-fro aortic murmur occurred in 12 cases, being purely diastolic aortic in only 3. The systolic murmurs were transmitted mainly to neck and shoulders, the diastolic to the apex, over the chest, up the sternum, or to the ensiform. The main features, then, were the aortic insufficiency with systolic and diastolic aortic murmurs and its accompanying water-hammer type of pulse.

Group III.—Aneurysmal.—Physical Findings.—The main features noted were heaving of the chest in 21; thrill in 7; tracheal

tug in 6; slight cardiac enlargement in 11; and broadened aortic dulness in 11. The fluoroscope and roentgen ray showed increase in the size of the aorta in 22, of the heart in 4; and pulmonary congestion in 1. In these cases there was an absence of bruits in only 3. The systolic aortic murmur was common, although murmurs were heard all over the valvular areas. Vocal-cord paralysis was a valuable finding.

In the comparison of the three groups the blood-pressure was of value, both from a diagnostic and prognostic standpoint. See Table I for the highest, lowest, and average of the systolic, diastolic, and pulse-pressure.

TABLE I

BLOOD-PRESSURE	SYSTOLIC			DIASTOLIC			PULSE-PRESSURE		
	Highest	Lowest	Average	Highest	Lowest	Average	Highest	Lowest	Average
<i>Group I</i> 16 cases Heart and mediasti- num	198	100	147	148	60	98	108	15	44
<i>Group II</i> 18 cases Aortitis	230	120	153	110	..	61	120	20	97
<i>Group III</i> 25 cases an- eurysm . .	210	75	R. 123 L. 141	100	60	76	110	17	52

It will be noted that in Groups I and II the systolic pressure averages higher than in Group III. In the aneurysmal group the blood-pressures in the arms were unequal and were difficult to take. It is noteworthy that the systolic on the left ran ahead of the right. In Group I we find a higher average diastolic pressure, which is of interest in view of the nephritic findings. These cases presented correspondingly graver clinical pictures. The average low diastolic pressure and high pulse-pressure in Group III suggested an aortic insufficiency, which was fairly well compensated.

While a high diastolic was generally found to have bad prognostic significance, one patient who had a systolic blood-pressure

of 165 and a diastolic pressure of 146 reported one year later that she was better. Another with pulse-pressure on the right of 108 and on the left of 10 reports he is feeling entirely well and is doing manual labor.

Treatment.—Much has been written on the various methods of treatment. Most of our patients, especially in the aneurysmal group, were not treated in our clinic; and therefore observations on the relative value of various measures have not been extensive. We have, however, followed certain general lines which seemed best for patients who remained for a time at the clinic. These may be classified as : (1) Rest; (2) cardiac medication; (3) potassium iodid and mercury, and (4) salvarsan and neosalvarsan.

Especially in the cardiac and cases of aortitis rest was found to be the most important factor, with such cardiac medication as seemed indicated. As soon as the most aggravated symptoms were in abeyance, mercury rubs were used in conjunction with potassium iodid in increasing doses by mouth. The use of intramuscular injections of mercury salicylate in at least two cases increased the distress and dyspnea, and its use was discontinued. Heavy doses of mercury given within a short time seemed to cause a reaction, possibly of local swelling, which increased the discomfort. The physician of one patient reported improvement with the use of protiodid of mercury by mouth. In 17 of the later cases salvarsan or neosalvarsan, or both, were used without any apparent bad result, and frequently with noticeable lessening of the discomfort. When the patient was quite sick, iodid of potassium and mercury rubs were always used before salvarsan was employed. In the later cases neosalvarsan was used in small doses in preference to the salvarsan. To our direct knowledge 34 of these patients received mercury or salvarsan or both, and 32 were given potassium iodid. Many of the remainder were given antispesific medication by their physicians at home. All those treated in our clinic received antispesific treatment except one patient who died. His trouble had lasted but two months, and was so severe that, in spite of a total inhibition Wassermann, mercury was not used. An autopsy was not obtained in this case, and we were unable to determine whether

there might have been some other causative factor aside from the syphilis.

A tabulation has been made of the patients treated at the Mayo Clinic, and followed by letters of inquiry.

TABLE II

STATEMENT FROM PATIENT	GROUP I (16 CASES) HEART AND MEDIASTINUM	GROUP II (18 CASES) AORTITIS	GROUP III (25 CASES) ANEURYSM
Alive four years.....	1
Alive three years.....	1	..	2
Alive two years.....	3	1	3
Alive one year.....	4	5	2
Feeling well.....	2 (12.5%)	1 (5.5%)	3 (12%)
Feeling better.....	5 (31.25%)	5 (27.7%)	3 (12%)
Feeling same.....	2 (8%)
Feeling worse.....	1 (6.25%)
Dead and not heard from.....	8 (50%)	12 (66.6%)	17 (68%)

Eight of the patients in the cardiac group improved; 1 died. Three were worse while under observation. Two of those who improved returned later much worse and died. In replies to letters from the remaining 13, 5 were better, 2 were feeling well, 1 was worse, and 4 had died; 1 was not heard from, and is probably dead.

Of the aortic patients, 10 were treated at the clinic and all improved, 7 quite markedly. One returned and died, and 1 died later after a resection of the pyloric end of the stomach for ulcer. Letters from the remaining 16 showed that 1 was feeling well, 5 were better, and 6 had died; 4 were not heard from.

Nine of the 25 aneurysmal patients were treated. Improvement was noted in 6; 1 died. Replies to letters sent to the remaining 24 stated that 3 were feeling well, 3 were better, 2 the same, and 5 had died; 11 were not heard from. From recent reports it was learned that of these, 2 who had definite bulging, heaving masses reported after two years that they are feeling quite well, although the masses have not disappeared; the other, who had an aneurysmal dilatation of the descending aorta, as shown by the roentgen ray, feels well and is doing regular farm work.

The ratios in Groups II and III are peculiar in that three

patients of Group III and only one of Group II are feeling well. Of Group I, 50 per cent. are alive, as against 33.2 per cent. in Group II and 30 per cent. in Group III.

SUMMARY

1. In 1379 cases of syphilis, clear-cut syphilitic disease of the heart or aorta occurred in 59 (4.29 per cent.).

2. The aorta seems to be affected by syphilis more frequently than the heart.

3. Syphilis of the heart does not present a typical syndrome other than that of myocardial change. The positive Wassermann is almost necessary for a definite diagnosis.

4. Syphilis of the heart, while presenting graver immediate symptoms, responds more readily to treatment, and the benefit is more lasting than in syphilis of the aorta.

5. Syphilis of the mediastinum presents a clinical history similar to that of cardiac syphilis, and also shows a similar benefit from treatment.

6. The use of potassium iodid with mercury is of value, even when the patient is showing marked evidence of decompensation.

7. The use of the iodids and mercury in some cases seems of value preceding the use of salvarsan.

8. Salvarsan, and especially neosalvarsan, is of considerable value in syphilis of the heart and aorta, and can be used in small doses, even in severe cases.

9. The use of vigorous and persistent antispecific treatment will relieve the discomfort, and apparently arrest the progress of certain aneurysmal cases.

SNUFF-POISONING*

EGERTON L. CRISPIN

The use of snuff, a most pernicious habit, with definite evil effects, has been creeping into this country in the last few years. Snuff in the form of pure ground tobacco has long been used in the United States; in the southern States it is chewed and used on snuff-sticks in the form of a paste. Furriers take it to expel the fine seal hair that gathers in the nose during the day's work; and the effect of such usage is probably not different from that of other kinds of tobacco.

There is another form of snuff, however, the effects of which are far in excess of that seen in the immoderate use of tobacco, that must contain ingredients other than the usual mixture of pulverized tobacco. This snuff, the so-called "Copenhagen," is sold and used extensively in the middle northwestern States by large numbers of foreigners, as well as American adults and youths.

References in the literature to the general use of this form of snuff are of comparatively recent date. Four years ago¹ attention was called to it as an evil in the State of North Dakota, and quite recently Hielscher² has presented a paper on the subject. Twenty-five cases have been indexed in the Mayo Clinic, none prior to 1914. The duration of the habit in some of these extends over a number of years.

The use of "Copenhagen" snuff produces most deleterious results. The users of excessive amounts suffer from chronic headaches, indigestion, irritable heart-action, increased respiration on exertion, and impaired mentality to the point of degeneracy. Delusions and hallucinations are not uncommon in the worst cases.

* Reprinted from *The Journal-Lancet*, 1916, xxxvi, 48-49.

A number of cases of marked psychosis have been observed in the State Hospital at Rochester, believed to be due to the excessive use of this form of snuff (Heyerdale³).

The habit is generally acquired through a friend who passes on a chew or a pellet to try, or by boys trying a pinch from sample boxes with which many of the smaller towns have been well sown. It is commonly used as a pellet placed under the upper or lower lip. Apparently it does not stimulate the salivary glands, as does chewing tobacco. The lack of expectoration and the invisible manner in which it can be chewed undoubtedly is a large factor in the growth and spread of the habit. The pellet is held under the lip until its effect is gone, and then replaced by another. The effect of the drug comes rapidly, evidently from absorption through the buccal mucous membrane. It stimulates and satisfies the craving that its use causes. In the novice it produces a marked dizziness, increased heart-action, and a "jag" feeling. The habit quickly grows; and in the chronic cases is most difficult to break. Attempts to cease its use leave a wrecked condition of the nerves.

Hielscher² calls attention to high blood-pressure as one of the conditions found in users of "Copenhagen" snuff. However, in our 25 cases there was but one with a blood-pressure that could be considered above normal for the individual,—systolic, 178; and diastolic, 115, —the only one recorded in which the systolic was above 150. The average in the series was systolic, 132; diastolic, 85. The average age of users is thirty-three and one-half years; the oldest, sixty-one, the youngest, twenty-two years. Fifteen of the 25 used alcohol, but 4 only in more than slight or moderate amounts. Thirteen either chewed or smoked tobacco. A few used from two to three boxes of the snuff a week; the majority, a box or more a day over periods from a year to twenty years, the average duration being six or seven years.

The chronic snuff habitué does not consult the physician to be cured of the habit, but because of impaired organic function. In none of the patients I have seen was the history of the use of snuff elicited except by direct questioning. They did not regard snuff as tobacco. The following are abstracts of rather typical cases:

CASE 141,168.—C. A. Examination September 14, 1915. Man, aged forty years; born in Norway; diamond-driller in iron mine. He had pain in the head, dizziness, etc.; gastric trouble off and on for six to seven years; no vomiting; no sourness or gas; heart-action very irritable; constipation. For three or four months he had "imagined" things, and was afraid in the dark. His face and general appearance indicated deficient mentality. It was difficult to obtain a history. His words were muttered; cerebration, slow and indifferent. He had used one or more boxes of snuff a day for seven or eight years. There was scarring and ulceration of the mucous membrane under the upper lip, where he carried his snuff pellet (Fig. 258). A couple of weeks after he had been told the cause of his trouble and advised to stop the use of snuff he wrote that he was unable to sleep and asked for medicine.



Fig. 258.—Ulcer of the mucous membrane of the upper lip

CASE 141,541.—O. M. A. Examination September 20, 1915. Man, aged forty-seven years; born in Norway; city salesman for wholesale house. He complained of "shooting pains all over, dizziness and stiff legs, indigestion, rapid heart, nervousness, and weakness." He stated that he had used snuff for five or six years; and in large amounts when drinking in order to allay nervousness. It sometimes made him feel good at first, but dopy later. After he began to take the "Copenhagen" snuff he used less tobacco. He started the habit by some one having him try it.

A box of "Copenhagen" a day equals about 30 or 40 small drinks of whisky a day to the habitual user. This snuff has a flavor different from other varieties, and is stronger,

There is much similarity in the symptoms of chronic poisoning in these cases. The snuff heart, the snuff indigestion, and, one might say, the snuffed mind show the serious effects of the persistent use of the drug. Ladd¹ quotes statements from a number of physicians to whom he wrote. They all severely condemn its use and believe the snuff to be doped. Their observations record the irritable heart, which Hielscher² refers to as the "Copenhagen heart," precordial pain, muscular weakness, cold sweats, eyes dull and stupid, destruction of the mental and moral fiber until self-respect and honesty are gone and the animal traits are in full force. Many boys from eight to eighteen years of age are said to be users. In an effort to combat what Ladd¹ calls "the greatest evil of the day," North Dakota has passed an anti-snuff law preventing the sale of snuff in the State.

"Copenhagen" snuff and "Right Cut" chewing tobacco are produced by the Weyman-Bruton Company. Each box has a stamped date. The users will not purchase old snuff, and the dealers do not sell it after it has overrun the date limit on the packages. This snuff has a peculiar odor, and is a moist, brownish substance, which soon dries to a powder when exposed to air.

Various conjectures have been made as to the presence of the foreign substance which causes the intoxicating effect. Physicians who have observed the effect believe it contains "dope" of some sort; but whether or not "Copenhagen" snuff is "doped" within the scope of the law makes little difference so long as the use of the mixture produces such apparent harmful effects. To be convinced of the increase in its use and of the evil effects, one has only to talk to the dealers, who state that there is an increasing demand and that they sell it chiefly to the laboring classes, for example, miners, lumberjacks, and farmers. One dealer in our own city said that he could spot nine out of ten of the snuff users when they came in the door. He had sold 50 boxes to one young farmer the day before.

CONCLUSIONS

The use of snuff seems to be on the increase. There is sufficient evidence for the conclusion that its use in appreciable amounts undermines the physical, moral, and mental health.

The nervousness, impaired health, and undermined moral fiber are a direct economic loss, and also it may be a factor in imparting to progeny a lowered resistance to the use of tobacco, drugs, alcohol, etc.

The manner in which the snuff is passed from one individual to another, the lack of external signs of its use, and the lack of information in regard to its deleterious effects, together with the active selling campaigning, are bound to cause the habit to spread and increase.

The scarring and ulceration of the gingival and buccal mucous membranes, with the long-standing chronic irritation, make these ulcerations in the snuff chewers probable sources of future trouble in which malignancy may be considered. It is to be hoped that more general recognition and publicity of the serious effects of the use of snuff will result in antilegislation to drive it from this State and all other States where it has a foothold; and also that publicity will serve as a warning to other States not yet similarly affected.

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THE EXAMINATION, PREPARATION, AND CARE OF SURGICAL PATIENTS *

CHARLES H. MAYO

The rapid advances made in medicine during the past three decades have necessitated many changes in the methods of general examination of surgical patients, and also in their preparation and after-care. Reviewing this period in the general practice of medicine and surgery, it appears that the methods which have survived are few, and simple in principle and application, as compared with the original methods. This includes all antiseptic surgery.

In medical practice there has been almost a revolution in variety and principles since we have come to understand bacteria and the diseases produced by them. We now know that most diseases arise from infection; and the acute condition or the late results of it are being treated. Briefly, the newer medicine is the understanding of the varying stages of the processes of infection, of the increased or lowered body-resistance, as well as searching for the local focus and aiding in its elimination. In this connection dentistry and diseases of the nose and throat have received much attention in the study of local foci of infections.

In regard to the patient: As a profession we are probably less acute in our general observation than was the practitioner of the old school. In his day everything depended on observation, and apparently no little thing was overlooked, whereas we are supported by many laboratories of special investigation. While it is possible in the present day to acquire a general survey of the practice of medicine in its various branches, it is wholly impossible for a physician to practise, and to apply unaided, the principles

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of the various laboratories and recognized specialties. For example, we are as dependent as ever on tests of the urine. Reports of albumin and casts, while intimating diseased kidneys, do not prove them essentially diseased, but lead the physician to search for the irritant in an acute or chronic infection, and to regard the kidney as an overworked eliminating organ; therefore, tests of renal efficiency have been developed.

Blood-examinations are not considered as infallible indications of special disease, as they formerly were, but the count, character, and color-index of the cells are of great value. Blood-smears and cultures are proving necessary to identify obscure infective conditions.

Laboratories for the study of bacteria, the preparation of vaccines and serums, and the examination of intestinal secretions, are also of increasing value. Intestinal parasites and bacteria often are found the cause of obscure general diseases other than the well-known tropical varieties. In the laboratories of research the specific effects of bacteria on animals in a study of the causes of obscure diseases is most important.

Radiography is invaluable in the diagnosis of diseases of the alimentary tract, diseases and fractures of bones, diseases of the lungs, kidneys, ureter, and bladder, and in locating foreign bodies, stones, etc. Radiography has the disadvantage of apparently being always correct in its evidence, and, even when contrary to the clinical findings, it is too often accepted as correct. Seldom, however, should a single, even though important, factor be taken to represent the true condition, but, rather, a detailed study of the various essential organs of the body. The body has a natural tendency to recover from disease. This is fortunate, since we are constantly overlooking conditions of which timely discovery would save much suffering and possibly life.

The electrocardiograph is of value in designating patients with heart-muscle changes who may die suddenly during the first few weeks following operation, from fibrillation, instead of embolism, as is often stated. The blood-pressure is also of value in showing the elasticity of the cardiac muscle and blood-vessels. Too much

attention is paid to a high systolic pressure alone; it is the relationship of the systolic and diastolic which gives the clue to the condition. Diastolic pressure 110, or higher, is of great importance in influencing the judgment of the surgeon. A high blood-count may mean diminution of fluid. This should be corrected if possible. Transfusion of blood before operation is rarely resorted to, but in extreme anemia from recent loss of blood, either directly after operation or in delayed accidental hemorrhages, shock is greatly relieved by the direct transference of blood to the patient. There are many methods of transfusion, the former direct methods giving way to the indirect, which are now simple and safe, and permit the transference of a measured quantity of blood. Hemolysis is a factor to be considered, and, unless the urgency is great, should be tested between the donor and the recipient.

The keynote of progress in the twentieth century is system and organization—in other words, “team-work.” This factor has been very noticeable in the medical progress of Germany, where true diagnostic hospitals have been established. Such hospitals conducted by the State through the medical department of its university would be of enormous value to the public and the medical profession in this country. Patients from all over the State could be sent by their home physicians to this hospital for diagnoses in rare, obscure, and complicated diseases. From these institutions patients could be returned to their home physician for medical or surgical care, with recommendations for such care, or be sent to special sanatoriums, or medical or surgical hospitals, as indicated. If returned to the home physician, included in the report of the case should be sent references of the latest literature on the subject and information of where such could be procured. Unquestionably, the appropriation for such an institution would readily be obtained if the public but understood the value and saving to the State which would come from the prevention and cure of disease. There is no general estimate on the value of human life as compared with the value of animals, consequently these facts are slower in being generally appreciated from a purely monetary standpoint.

The starvation diet in the preparation of surgical patients has long been abandoned, the dangers of acidosis being nearly as great in starvation as in diabetes. The diabetics are accepted as a risk, and, except in emergencies, are always given preliminary treatment for their general condition, endeavoring to maintain the alkalinity at a high standpoint. The condition of children is improved by sugar and other glucose foods.

It should not be forgotten that treatment aids many patients more effectively before operation than after. Those who are suffering from starvation, loss of blood due to acute or delayed obstruction of the alimentary tract, should have a two-stage operation when possible. For example, in a case of pyloric tumor with obstruction the body fluids should first be restored by enemas, liquid nourishment, and subcutaneous injection. Gastro-enterostomy is then done; and, after two or three weeks, when the patient is greatly improved, a pylorectomy is made, both operations being accomplished with greatly lowered risk to life.

Physics are less freely used than formerly. Because of their great depletion of the body-fluids and the fact that they disturb rest, laxatives should be given two or three days preceding the operation, instead of the night before.

There probably has been no more noticeable change in the preparation of patients for operation than that of preparing the skin. The old methods of applying soap poultices for several days so lowered the resistance of the skin to germ life that the area for operation was often a mass of pustules, a condition seldom seen in emergency operations. The present-day method of iodine application and similar rapidly acting agents has almost eliminated such infections. With these superficial cleansing methods, however, much care is used to protect and cover the skin about the incision during operation.

THE AFTER-CARE OF SURGICAL PATIENTS

More attention is now given to relieve the suffering of surgical patients, at least during the first and second days after operation,

by opiates and sedatives. These are not carried to the extent of obscuring the pain as a symptom of serious complication. Senn is quoted as having said that "when the last suture is tied in abdominal surgery the fate of the patient is sealed," a saying which is not true to-day, for many patients are saved by reopening the abdomen for late hemorrhage or for obstructive conditions of the alimentary tract. Enterostomy made at the end of the third day from the commencement of obstruction has saved many lives; if done later, the results are not so successful. Patients in poor nutritional condition may be tided over temporary periods of gastric paralysis by jejunostomy. Dilatation of the stomach following abdominal operations is more common than was formerly supposed; however, if discovered early, it may not be serious. If patients are not doing well, even if they do not complain of the stomach, a tube should be passed. Should there be dilatation, caused by paresis, the stomach should be emptied every six or eight hours until relief is obtained. If intestinal obstruction occurs, it may be relieved by enterostomy as late as the night of the third day or the morning of the fourth.

Primary infection now rarely occurs in clean cases. A dry wound with a light dressing held by adhesive strips is the rule. Delayed infection, formerly attributed to catgut, we now know to be frequently caused by a dead space in which a blood-clot has become infected by bacteria carried through the vascular system from some local focus. These, however, should be classed among the preventable troubles. Large amounts of antiseptic catgut, used as sutures and ligatures in a limited space, become a menace from the chemical irritation, and the consequent excessive secretion, of the wound, such excessive secretion being nature's method of washing out the antiseptic preparation before the phagocytic activity of the leukocytes has developed.

Induration of the wound should be looked for in patients with slowly rising temperature after five days, and, if found or suspected, should be opened by puncture.

Much benefit comes from the intelligent use of bacterial serums and vaccines in chronic diseases. If not effective, they are not so

much to be discredited as is their preparation, selection, or employment.

When patients are compelled to remain in bed for a long time, they should be turned and moved as much as possible. They should also be urged to keep their limbs moving as much as their position and condition permit, which aids markedly in inhibiting muscular weakness occasioned by prolonged rest.

Getting patients out of bed as soon as possible after operation conserves strength, improves the mental attitude, prevents the lowering of blood-pressure and the change in the heart-muscles, and apparently has reduced the percentage of sudden deaths from embolism. The sooner patients can be removed from the depressing influence of general hospital life, the more rapid their convalescence.

ERRORS IN ANATOMIC DEVELOPMENT: THEIR CAUSE AND SURGICAL SIGNIFI- CANCE *

CHARLES H. MAYO

Errors of development are always of exceeding interest, some of them because of rare or curious features of the deformity and others because of their serious or fatal import. Only when studied in large numbers does one find these deformities occurring in a manner so regular that scientific interest in their causation is aroused, and the fact is quickly appreciated that errors of development occur in the cleavage-lines of advance from lower to higher forms of life.

Many anomalies are seen in domestic animals; those occurring in the lower forms of life usually perish in the struggle for existence. Those occurring in the human family may be remedied or the life of the individual may be preserved by care. The superiority of the vertebrate over the invertebrate lies in the extraordinary development of the nervous system, and for one-third of the gestation period it represents one-half of the body growth. The change of the invertebrate to the vertebrate not only concerns the nervous system, but is just as important in the intestinal system and in the organs of nutrition and elimination. Anomalies of these structures which represent the superiority of the vertebrate are fraught with the most serious consequences.

Of much less serious import are most errors associated with variations in circulation that are not primarily incompatible with life. This is also true of errors due to inclusion of the elements of

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the skin in the midline, leading to the development of simple dermoids as well as to failure of union of the branchial clefts, which represent the gills of the fish type.

In searching for cleavage-lines in the process of development it is usually easy to follow changes that have occurred by comparing animals of nearly similar types. This is a long step to the development of man; nevertheless the tracing has been gradual and the gaps filled, so that the missing link from animal to man is neither mysterious nor so far removed as the tracing of similar changes among lower animals of the distant past when new types which still persist appeared from time to time. This has been especially true in the great change from invertebrate to vertebrate. All progress has been identified by such changes in the predominant species of any period which has enabled them to live in a different medium and to be sustained by different nutrition. Thus from sea life came the amphibians, in some of which the swim-bladder changed into primitive lungs; others respired by the skin. Occasionally changes have occurred through the degeneration of the predominant species; in this manner the tunicata developed.

In a consideration of the causes of errors of development it is useless to study the changes in vertebrates alone, as during one-third of the period of gestation the vertebrates are almost alike in their development. In following the forms of life from the most primitive types, it is seen that the higher only have opportunities for many abnormalities, and that man has the greatest assortment, since abnormality of mind must be included. Consequently such a study forces the student back to a consideration of invertebrate life.

In the higher invertebrates, such as the limulus, the peculiarity of development was a single straight gut connected with a cephalic stomach; the nervous system consisted of special sense-organs, olfactory and optic, the supra-esophageal nerve ganglia connected with the infra-esophageal or segmented nervous system by the esophageal commissure, the latter acting similar to the crura cerebri of man. The shell or chitinous membrane is like cartilage

in man and so also is the comparison of glands and organs of special sense. These species, having a nervous system which surrounded the gullet, were necessarily limited as to their development since the greater their nervous system and ability to find and catch their prey, the less their ability to eat it and they became the blood-suckers. The peculiarity of the nervous system, however, was such that it grew over the cephalic stomach exactly to conform with the growth of the nervous system over the ventricles of the vertebrate brain. Between the collections of nerve-tissue on the cephalic stomach are placed masses of digestive glands which resemble the cells of the liver and pancreas. In these higher invertebrates the digestive action is limited because of the high type of food ingested.

The invertebrate has a nervous system in front of the intestine, while the vertebrate is characterized by having the intestinal system in front of the nervous system. Some students, led by Hilaire,¹ have claimed that the change from the invertebrate to vertebrate required that some lower type of life should reverse the surface and start swimming on its back, the ventral becoming the dorsal, the mouth also changing position. It seems impossible to explain the reversal of the nervous and intestinal systems in any other way unless Bateson's² simple theory is accepted, that they developed from the beginning as two types, one with the nervous system in front of the intestinal tract, the other behind. The later, more tenable theory of Gaskell³ has grown in favor and explains these changes along lines of limitation of type as variations of body-structure necessitated radical changes to maintain progressive development.

If one considers the structure of the nervous system and its ventricles, the central or neural canal and its terminus in the first period of gestation, he will find that it is almost exactly like the cephalic stomach and straight gut of the invertebrate. The infundibulum as a tube connects the third ventricle with the ventral surface exactly in the same position with reference to the spinal ganglia and special sense-organs, so that one might speak of this structure as an esophagus connected with the cephalic stomach;

while at the caudal extremity, through the neuro-enteric canal, it is connected in the human embryo during the first weeks of life with the rectum just above its outlet.

The gullet of the invertebrate disappeared within the skull, taking with it the pituitary gland, the area thus vacated being marked in embryonic life by a pharyngeal depression called "Rathke's pouch;" this marks the site of the invertebrate mouth. The thyroid went down through the tongue to its cervical location. Both of these glands had to do with development, stature, nutrition, and sex.

The pituitary did not develop from the infundibulum as it exists in the same position on the esophagus of the invertebrate. In the region of the infundibulum and of the hypophysis, because of developmental change or reversion, theoretically should be found the same types of tumors (that is, dermoids, cysts, and teratomas) as are found at the caudal extremity of the neural canal which has also lost its opening. It is a satisfaction to state that such have been reported by several observers, among them Hecht,⁴ who reported a dermoid, and Cushing⁵ a dermoid and cysts.

By such change the cephalic stomach and straight gut disappeared to become the ventricles of the brain and neural canal, which necessitated the ventral development of an intestinal system and the upward and backward growth of the segmented nervous system surrounding the spinal canal. The neural canal in the human embryo is lined by a single row of ciliated columnar cells, the cilia of which disappear at the third month. The nerve-cells are arranged in regular groups over the cephalic stomach and, becoming bunched or approaching each other, infold the membranous area between them which becomes the choroid plexuses. In the limulus, the highest invertebrate, the membrane between these groups of nerve-tissue is covered by cell-bodies which resemble those of the liver and pancreas and aid in the moderate digestion required for the assimilation of very highly developed food. In ammocetes, the lowest vertebrate, the vestigial remains of such degenerated structure are seen covering a portion of the ventricles between the

gray matter and, as shown by Gaskell,³ enables a small brain to fill a cavity otherwise too large for it. The cerebrospinal fluid is formed as a secretion of the choroid plexuses and is found filling the ventricles and neural canal in the third month of the human embryo, which shows the period of the closure of these spaces. This fluid passes through the main iters which connect the various ventricles and filters through the thin membranes of the brain and cord, equalizing the pressure at all points. To maintain equilibrium of pressure, the absorption is carried on by the pacchionian bodies and a limited lymphatic system, the great bulk, however, being carried by the veins of the arachnoid space.

An increase in the tension of the cerebrospinal fluid may be caused by loss of equilibrium between production and absorption of fluid; vestigial remains of the old digestive glands of the cephalic stomach might be stimulated into activity by chemical irritants or food. This increase in fluid has been experimentally produced by blocking certain iters and by the injection of certain irritants into the ventricles. It also appears through the growth of tumors. Treatment of the axolotl and frogs in their earliest development with 0.7 and 0.6 per cent. salt solution seems to cause the frequent appearance of spina bifida. Spemann,⁶ by suture-injury of lower forms of life, created double-headed monsters. Stockard⁷ repeatedly caused Cyclopean monsters to develop from artificially fertilized eggs treated with magnesium chlorid. Mall⁸ reports many examples of artificially developed monsters, showing that monsters appear from interference with the germ, the egg, or foetal development.

In the vertebrate brain, including the human, a pineal body represents the vestigial remains of the third eye found in some of the invertebrates. Cranium-fused monsters may have a fused third eye, but the true Cyclopean eye must come from the pineal body. Such monsters are rare and incompatible with life, as the cerebrum is necessarily nearly or quite missing.

Inasmuch as all life originally developed in sea water and, as stated before, the progress in the development of animal life having come from its ability to change the media in which it lived by a new

development or change in its structure, one can readily understand how salt solution or magnesia might inhibit the development of that structure which had changed to enable existence in a different medium. This is undoubtedly one of the reasons why sea life leaves the medium in which it lives to spawn. Salmon are a high type of fish and they spawn in fresh water; theoretically, treating their eggs with sea water should cause errors in develop-

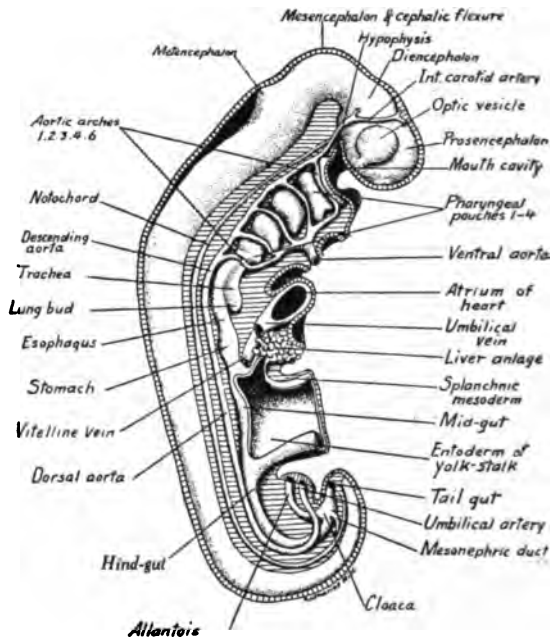


Fig. 259.—Diagrammatic reconstruction of a 4.2 mm. human embryo viewed from the right side (adapted from a model by His) (Prentiss, "Embryology").

ment reverting toward the parent stock. All things in nature have a reason for their occurrence, and this is undoubtedly an example. May it not explain the action of the parathyroid bodies that are supposed to maintain the stability of the mineral salts?

Anomalies of development of the spine and head are associated with overproduction of fluid or its escape, as seen in hydrocephalus or anencephalus. Midline cranial tumors of the meninges alone

or including brain matter are seen with all degrees of failure to close, even the entire neural canal posteriorly remaining open. This is known as rachischisis—small openings with protrusion of membranes or including portions of the cord down to the spina bifida occulta, in which the opening and protrusion without persisting tumors prevented the development of bony covering during embryonic life. These areas are marked by thickened tissue, including the skin, which has an excessive local growth of hair.

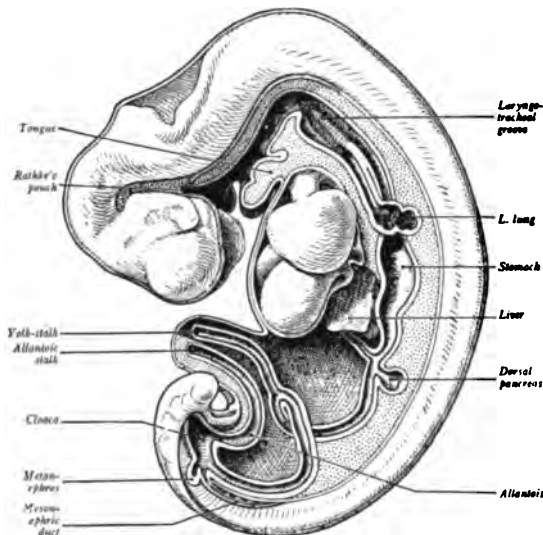


Fig. 260.—Reconstruction of a 5 mm. human embryo showing the entodermal canal and its derivatives (His in Kollmann's "Hand atlas") (Prentiss, "Embryology").

Formerly these conditions were attributed to failure of the bony canal to close, permitting the protrusion to occur; but they are due to an excessive development of fluid, with protrusion of the membrane, which prevents development or union of the bony covering.

Anterior meningocele is rarely seen. Those noted have usually been in females and have caused obstruction of the alimentary canal by filling the pelvis. Nearly all such persons have died when operated on. One case has been reported from our clinic with

recovery. The majority of spina bifida occur in the lower region because of the late closure of the lower end of the neural canal. These may be pure meningoceles or may contain also cord elements and may then be associated with varying degrees of talipes, occasionally accompanied by paralysis of the sphincters. Moore's⁹ statistics of reported cases show 23 per cent. of spina bifida to be sacral, 34 per cent. lumbar, 29 per cent. lumbosacral, 4.5 per cent. dorsal, 9.5 per cent. cervical, and two cases were occipital.

In hydrocephalus and spina bifida more careful study must be made of the choroid plexuses for vestigial remains of a digestive apparatus; also, in spina bifida and rachischisis the central canal, the "area medullo-vasculosa" of von Recklinghausen, being open and having the appearance of mucous membrane, must be analogous to the invertebrate intestine.

In the earlier development of the vertebrate the nervous system is much longer than the notochord from which develops the spinal column of the higher vertebrates. The neuro-enteric canal closes in the third week of gestation. This, with some of the posterior rectal tissue and its own nerve-tissue, becomes atrophied to a small mass known as the coccygeal body at the end and inner side of the coccyx, which is often the center of true or neurotic complaint. The neural canal is attached to the posterior surface of the coccyx and steadies the spinal cord, the lower neural canal becoming a firm filament known as the "filia terminalis" extending from the coccyx to the end of the spinal cord, somewhere between the first and third lumbar vertebræ. The filament and the cauda equina are produced by traction from the rapid growth of the spinal column which, from being originally shorter, outgrows it one-third.

All that is known of the causation of talipes has been the association with lumbar involvement of the cord by varying degrees of spina bifida. To make progress in the study of its causation the lumbar enlargement of the cord must be examined for evidence of increased development of fluid late in gestation or for a separation of the attachment of the terminal filament, causing undue traction on the nerves of the cauda equina. Spina bifida occulta should be

looked for in talipes, a condition in which a beginning spina bifida would be sufficient to prevent completion of the bony covering of the cord and, then receding, leave an adhesion which, from the rapid growth of the spine, causes destruction by undue stretching of the posterior nerve-tracts to the legs.

The roentgen ray will show these bony deficiencies and surgery may yet have much in store for these sufferers in the way of dividing bands and freeing adhesions. Work along this line has been

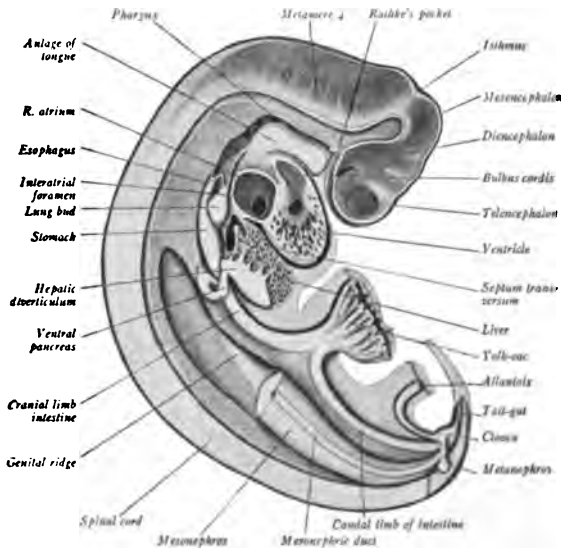


Fig. 261.—Median sagittal dissection of a pig embryo of 6 mm. to show viscera and neural tube (Prentiss, "Embryology").

done by Jones¹⁰ and by Sever.¹¹ In this connection scoliosis in theory should be due to a failure of proper development of the notochord from which, by segmentation, spring the bodies of the vertebræ. This may be intrinsic or due to faulty development of the segmented nerves which surround the neural tube.

Dermoid tumors, sacrococcygeal in type, are very common and are caused by the rapid growth of the spinal column producing traction on the neural canal which originally reached to the skin of this region. Here also are found the teratomas from the

coccygeal body. These tumors contain mucous membrane from the post-anal bowel, nerve-tissue from the neural tube, bone and cartilage from the coccyx, and various inclusions of surrounding tissue. Some of them have mucous cysts lined with ciliated epithelium from the neural tube, showing the misplacement of tissue to have occurred before the third month of gestation.

In the development of the new intestinal system from the yolk-sac it divides into fore, mid, and hind gut. At the pharyngeal end

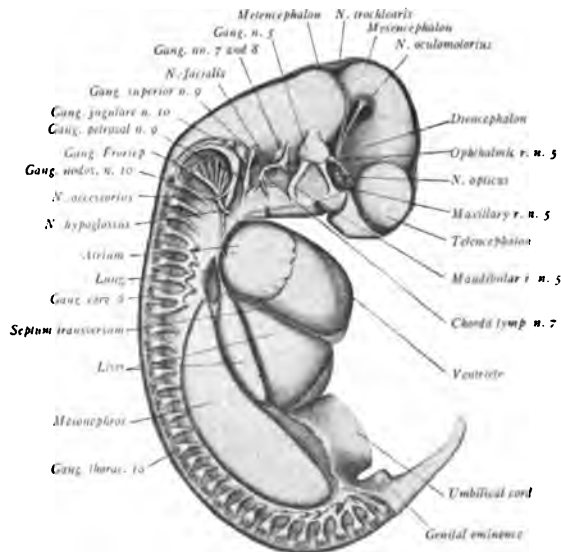


Fig. 962.—Lateral dissection of a 10 mm. pig embryo showing the viscera and nervous system from the right side. The eye has been removed and the otic vesicle is represented by a broken line. The ventral roots of the spinal nerves are not indicated (Prentiss, "Embryology").

this divides into an esophagus and respiratory system. At an early period in the cavity of the stomatodeum (developing mouth and pharynx) the pharyngeal end is closed by a membrane of entoderm and ectoderm separating the esophagus and trachea from the pharynx. This disappears about the fifteenth day, its persistence being almost unknown. In this region are found certain failures of union of the gills or branchial arches and fissures, causing harelip, cleft palate, branchial cysts, and similar defor-

mities. The thyroid, passing between the three portions of the tongue in its development, comes to rest astride the trachea below the cricoid cartilage, and its anomalies consist in the remains of all or part of it in its lingual position and in the separation of embryonic pharyngeal mucosa, causing midline thyroglossal duct-cysts. These are located about the hyoid, often passing through a small opening in its body over or under it to a pocket behind. They tend to recur after operation unless searched for and removed.

At the caudal end of the body there is a most interesting group of anomalies. In early fetal life the developing bladder and rectum are one. The anterior portion of the cloacal cavity consists of the allantois and Wolffian ducts, from which are developed the sex organs and the urinary collecting system. The kidney-secreting substance extends as mesothelial bodies or nephrogenic tissue from lower dorsal down to the second sacral vertebra. They lie close together, with the aorta between. This substance is supplied by many blood-vessels derived from a delicate plexus surrounding and connecting with the aorta. From a pouch which early appears from the lower portion of the Wolffian duct are developed the ureter and pelvis of the kidney. This collecting portion becomes attached to the secreting portion by climbing up the ladder of the blood supply, so to speak, of the nephrogenic substance. The numerous blood-vessels drop off and enlarge as the pelvis of the kidney ascends to its higher position, and the secreting substance arranges itself over it and forms a capsule. The two mesothelial bodies may touch each other and become fused, developing the horseshoe kidney or various attachments, 90 per cent. of the horseshoe kidneys being fused at the lower pole. Some of the mesothelial or secreting portion of the kidney may not become connected with the collecting portion, and may then retain its embryonic type, forming a mesothelial rest from which may develop so-called "hypernephroma," or, more correctly, mesothelioma of the kidney (Wilson¹²). In other cases a failure of connection between the secreting portion with the collecting cavity and continuance of secretion without elimination form a congenital cystic kidney, usually double.

Wherever the kidney stops in the process of union of collecting and secreting portions, its renal artery develops from the major supplying it at the time. As growth continues, the delicate vascular plexus outside the aorta disappears and the renal artery comes directly from the aorta; but owing to change in position it may come from a lower position on the aorta, the sacral artery, or from the common iliac. The malposition of the kidney is not so serious if it can but carry on its function, but malposition may lead to injury. Excessive mobility is not a disease unless the renal function is interfered with or the kidney in its movements disturbs some other organ; thus the movable right kidney may disturb a diseased appendix, the appendix, however, being the primary offender. Mobility may interfere with urinary delivery by kinking the ureter over a band of connective tissue or an anomalous artery which occasionally is seen connecting the lower pole of the kidney with the aorta, one of the original mesothelial vessels which failed to disappear. One kidney may be missing from a failure of development of the mesothelium—the secreting structure. Three or four kidneys may be present with three or four complete ureters or partial ureters. Splitting the collecting portion at the Wolffian duct causes double ureters and fused or separated double kidneys on one or both sides. The division of the pelvis into several tubes connecting with one or two ureters is normal in the otter and beaver.

Occlusion and constriction of the urethra occasions various forms of maldevelopment in the male known as hypospadias and epispadias, with terminology according to the extent and character of the cleft and the location of the external opening of the urethra. Slight malformations of the terminal portion of the urethra are not uncommon. Exstrophy of the bladder, hypospadias, and similar deformities are undoubtedly caused in a manner similar to spina bifida, by secretion at an early period, the blockage of exit causing a like separation of bone from interposed tissue and in exstrophy of the bladder preventing the formation of the pubic arch. Persistence of allantois with but partial development of the urachus, causing a secondary bladder or cyst between the um-

bilicus and the normal bladder, is occasionally seen. During this time the cloaca is being divided by a partition into rectum and bladder, and the proctoderm forming the anal depression should join the lower rectum. The latter process sometimes fails of completion, the anus remains imperforate, or the rectum is connected with the bladder of the male or the genital passage of the female through the cloacal connection.

From the paired manner of its origin, the uterus may fail of development into a single body, each half remaining a separate organ or becoming partially fused and connected with its ovary and tube. The genital passage also may be double or single in association with such deformity, all of which conditions are normal in various vertebrates. There may be absence or atresia of the genital passage, causing retained secretions within the distended uterus. Rarely all the genital structures except those connected with the ectoderm may be missing in the female. In the male the generative glands may be missing on one or both sides. They may remain within the abdomen or may be arrested at any point in the canal during their descent. The gubernaculum is probably not an active structure, but merely steadies the generative glands while the body and limbs grow away from them.

In the caudal region are developed higher forms of dermoids than those of inclusion of skin. Such tumors have bone and tooth formation with hair and skin, and are considered to have arisen from blastomeres by some investigators; from fertilized polar bodies or fertilized but imperfectly developed ova included within a normal one by others. There are also the theory of totipotent cells, and Shattuck's¹³ theory that ovarian dermoids arise from a transmission of the fertilization to fetal cells in the developing ovary of the embryo.

In its early development the large bowel lies wholly on the left side of the spine, and rotates around the superior mesenteric artery as an axis, the cecum at the third month being under the stomach, later under the liver, and finally to the right iliac fossa. The surgical importance of this is that all the important blood-vessels and nerves are on the inner leaf of the mesentery; the outer

can be freely divided. All of the large bowel may remain on the left side of the spine through failure of rotation, or the cecum, by partial rotation, may come to rest at any position between the right iliac fossa and its place of origin. This is of importance when appendicitis occurs in such conditions. Because of the late descent of the cecum, fetal membranes develop over it and about the ileocecal valve. Rotation may involve the mesentery of the small bowel, causing extensive strangulation, as shown by Keith.¹⁴

Persistence or failure of absorption of the union of the bowel with the cord as developed from the yolk-sac causes the various forms of Meckel's diverticulum. When adherent, these diverticula are a source of danger because of their liability to cause intestinal obstruction from loops of bowel becoming strangulated beneath them.

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INFECTION A CAUSE OF LOCAL AND GENERAL DISEASE *

CHARLES H. MAYO

For the past ages of which there is any record, medicine has always been surrounded by more or less mystery, in some periods and among many people being closely associated with whatever religion or form of worship then held by them. Unfortunately, much superstition is still connected with the science in the minds of many. When one reviews the past of medicine, what little has been preserved of the writings of the earliest medical men whose names are honored shows a remarkable insight into the practical side of life. The delicate surgical instruments recently excavated at Pompeii show that, two thousand years ago, men were capable of inventing and using them. Skulls from four to six thousand years old show round and square trephine openings, and this is true of the skulls of certain mummies two thousand years old found in Peru and southern Central America.

From observation and autopsy the practice of medicine has developed, but as people often died of complicating or intercurrent disease, it was then too late to complete the records, and deductions were not always correct. Medical men of the past were, of necessity, keener observers of their patients' symptoms than the physicians of the present, since everything depended on such observations. Slight symptoms, seemingly almost unimportant as thought of today, were to them like straws, showing the direction of the wind.

When surgery of the head, chest, and abdomen became possible,

* Abstract of paper read before the Chicago Medical Society, November 17, 1915.

and sight and touch could aid our investigation in the living, the science of medicine advanced by leaps and bounds, and this has come within a generation. During the last one hundred years more than twenty years have been added to the average length of human life; twelve of these years have been added during the last three decades. The Public Health Service has had much to do with this advancement, through its campaign of education in hygiene and the so-called "preventive medicine." As a result, there has been a great reduction of mortality in children, and consequently more people coming to middle age, which is a very important factor in the reported increase in the occurrence of cancer. There is also an enormous number of people saved by surgery as compared with one hundred years ago.

Vaccination against smallpox has been employed for centuries in India and China; it was accidentally discovered and empirically used. The first record of its application in Europe was in Belgrade, Serbia.

Lister did not develop the theories of germ life, but he was the first man of note to grasp the wonderful importance of Pasteur's work and apply it to surgery. While his methods were complicated and crude, they served their purpose and stimulated thought on the subject. Many of the methods were soon replaced by simple and more effective ones, making possible the ever-increasing development of surgery and bringing the eye to our aid in viewing disease conditions in the living, supported by the microscope in the study of the invisible.

How curious it is that Hahnemann and his school came so near these great discoveries and just missed them in their doctrine of *similia similibus curantur*. Their efforts were bent in the right direction, but were limited to the use of drugs which modern medicine is reducing to but few in number, as compared with the past, and these having definite effects on the circulation, the nerves, and the body secretions. The whole trend of medicine has turned toward a study of methods of repair of the body tissues and fluids, all efforts being made to favor the development of resistance.

How glorious was the death of the men who lost their lives in a study of those bacteria which lived for a time in an intermediate host, and how simple now is the prevention of such diseases as yellow fever and malaria by the destruction of the mosquitos and shutting them out by a screen, the control of typhus fever by mere body cleanliness in keeping free from vermin, and, where cleanliness is impossible, as in war, by the use of serums. The antityphoid serum has proved of enormous value in the prevention of disease by developing an immunity against the dangers of impure water to which travelers, and especially soldiers, are necessarily exposed.

The next advance was the realization that the germs of disease actually live in the blood, which was appreciated in the past as occurring only in pyemia and septicemia. A drop of blood from the ear in pneumonia cases cultured early in the disease will show a pneumococcus growth almost as soon as the disease can be surely identified by ordinary methods, and more surely in the obscure cases. Warfare on bacteria which float freely in the blood is exceedingly difficult, except as it is carried on in the peripheral circulation and in the local areas where the disease is active, and which we identify as the local manifestation peculiar to typhoid, pneumonia, measles, smallpox, or other diseases.

Where did the next advance in medicine come from? It came from the results of the work of such research investigators as Rose now, who has proved conclusively that many or most of the so-called local diseases, such as appendicitis, cholecystitis, and ulcers of the stomach, are bacterial in origin, and that the attack on the mucous membrane is not on the surface, but through the blood as a destructive infarct, the bacteria being carried by the circulation to the base of the mucous glands—the unprotected rear, so to speak. These conditions can be experimentally reproduced. For example, after removal of an appendix filled with pus a culture is made which shows colon infection, the appendix is opened, washed, seared in a flame to destroy surface bacteria, crushed or ground to a fluid state, and a culture from this material will often show a diplococcus or streptococcus as the real cause of the disease, the

exudation from which had become inoculated by the colon bacillus to which it was freely exposed. This culture injected into the veins of one of the few animals having an appendix, the rabbit, will in two-thirds of them produce lesions in the appendix, such as hemorrhages, erosions, and various forms of destruction of the mucous membrane. In nearly one-third of the animals there will be no change, the bacteria being destroyed or eliminated before reaching the location of this particular environment. In those in which there is a result, the appendix is the organ most commonly involved, though not necessarily the only one, as in some there would be infarcts of the kidney, effusion in the joints, and myocardial changes as various side lines of associated inflammation. This is true of diseased gall-bladders and excised ulcers of the stomach and duodenum, as well as joints in rheumatism. That these infections are variable and multiple is explained by the studies in rheumatism and reproduced rheumatism. The pneumococcus and *Streptococcus hæmolyticus* and *Streptococcus rheumaticus* and *Streptococcus viridans* have been made by Rose now to change or transmute from one to another by changing their environment. This greatly simplifies our study of bacteria and our appreciation of disease, both general and local, as by it we accept the fact that the pathogenic bacteria of varying degrees of virulence have their selective affinity because the tissues involved afford an environment similar to that from which they came. It may soon be proved that diseases of the nerves, like sciatica, tic douloureux, herpes, neuralgias, and similar disease arise from bacteria distributed by the blood from small foci of infection more or less under tension, as in the tonsil, at the root of teeth, or a blocked nasal sinus.

Relapses occur from the chronic character of the trouble, which break down instead of increase the immunity, as anaphylaxis. Through the occasional slight delivery of these toxins there is an increase or relapse in the local manifestations, just as is seen in a local tuberculous process from the use of tuberculin in an effort to increase tissue resistance. In this line should be included the infections of the respiratory tract, such as asthma, pneumonia,

and lesions of the valves of the heart. In asthma wonderful success has been reported from the removal of local foci of disease affecting the respiratory tract. From open surface infections, such as pyorrhea, open diseased tonsil crypts, open sinuses, and bacteria absorbed from the large bowel come rheumatoid troubles and joint deformities. It has been proved too often to be a mere coincidence that the therapeutic elimination of bacteria from the large bowel or the removal or short circuiting of large sections of the colon in constipation has produced wonderful results in the cure of rheumatoid arthritis. Years ago Metchnikoff stated that he thought the large bowel was a mistake, and that human life would be lengthened by its removal, stating that the toxins of its bacteria was a cause of endarteritis, and that it probably had more to do with advancing age than time.

The reports of research work by foreign investigators, especially that of Poynton and Paine, most of which has been based on autopsy, and in our country the numerous investigators, such as Dick, Davis, and others, in several fields of research, and especially the work of Rosenow in these lines, have marked a definite path for the future of medicine. We have long and vaguely connected certain inflammations of the iris with rheumatic troubles, more directly have associated certain inflammations with gonorrheal toxins, the direct connection being evident, and it has long been said that lues may simulate almost any disease and affect all the tissues of the body; thus obscure lesions have often been attributed to this cause. We now know that the specific living bacteria starting from a central focus traveling in the vascular system makes secondary deposits in these various tissues of the body according to their affinity. The side lines of involvement are due to some variation in culture of apparently specific types of bacteria, but the main or essential manifestations can be reproduced in the animals over and over, showing a definite percentage of localizations in similar tissues from cultures carried from man to animal. Rosenow is able to induce inflammations in the appendix of rabbits from strains of human appendicitis in 68 per cent. of 68 rabbits injected. From strains grown from ulcers of the stomach and duo-

denum, inflammations, hemorrhages, and ulcers were developed in 75 per cent. of 103 animals injected, while bacteria grown from inflammations of the gall-bladder produced lesions of the gall-bladder in 80 per cent. of 41 animals injected. Of course, many side lines of infection were also seen. These are but a few of the many diseases that we have long considered local entities, and which now must be classed as a result of secondary lesions derived from a small original focus some place in the body. As to the local foci of infection, there have been found nearly 60 varieties of bacteria in the mouth: normally there may be but a few to a dozen types. We have about the teeth, pyorrheas, cavities, blind or apical pockets, open crypts, or buried pockets in tonsils where bacteria are commonly harbored. Such tonsils are not necessarily enlarged; teeth with apical pockets may have no pain and look normal, but the roentgenogram will show these cavities very distinctly. The strains of bacteria delivered to the vascular stream may in one case affect the iris or cause retinal hemorrhages, in another cause ulcer of the stomach or duodenum or cholecystitis or appendicitis, a Fallopian tube inflammation, or a joint involvement. As known in man and proved in animals, one or two secondary foci of infection may be derived from the same strain which would necessitate, under present conditions of examination, the patient being required to visit specialists in the various fields of medicine, while a good dentist or throat specialist would have cared for the local focus and effected a cure unless the secondary lesion had produced local destruction of tissue, resulting in permanent impairment of function. How long are we to continue to talk about uric acid in rheumatism? The crying need today is for more diagnosticians and better team work in diagnosis hospitals. We have been too long dealing with end results of local foci of infection as entities as a result of erroneous deductions from autopsies, instead of a study of disease conditions in the living.

STUDIES IN THE ETIOLOGY OF CANCER

VI. FACTS VERSUS SPECULATION IN THE PROFESSIONAL CONCEPTION OF CANCER *

WILLIAM CARPENTER MACCARTY

That there is an unsettled condition of the professional conception of cancer and that this condition is the result of incomplete observation and speculation, are perfectly clear to any student who has carefully compiled the literature on the subject.

The cancer problem involves four distinct considerations: first, the question of how cancer develops (histogenesis), second, why cancer develops (etiology), third, how cancer can be prevented (prophylaxis), and fourth, how can cancer be cured after it has developed (therapeutics). The discussion in this paper will deal only with the first of these four questions, namely, the histogenesis or development of cancer.

Perhaps the best method of realization of the chaotic conception, which undoubtedly exists, is to review the published expressions which are utilized to explain cancer and other tumors. Thus we find the development of tumors spoken of as: An inherited pathologic quality of cells; a failure of cells to differentiate; a disturbance of the idioplastic formation of cells; the formation of a "new race of cells"; a prenatal separation of cells; a postnatal separation of cells; a primary inherited change in the nature of cells; a change in the biologic behavior of cells; a product of connective-tissue senility; a specific tumor diathesis; a nutritional disturbance of the equilibrium of vegetative and functional cell

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power; a change between the relation of nerves to cells; a reduction of the avidity of the body-cell; a primary emancipation of cell growth from the normal laws of growth; as cellular atavism; a return to the embryonic condition of cells; an inherited or acquired intracellular abnormal metabolism; a cessation of the regulating growth influences of cell differentiation; a heteroplastic change of the fixed connective-tissue cells; a prenatal separation of cells; as congenital anlagen; a release of the organic connection of cells; a separation of germinal cells; an embryonic separation of cells; a shunting of germ-cells from their normal relations without misplacement; superfluity in the development of cells or tissues; as separated germ-cells; misplacement of cells, and an abnormal persistence of embryonic cells. This multiplicity of explanations in itself indicates dissatisfaction with the lack of accurate or scientific knowledge which we possess relative to the condition.

The three fundamental things in life which make that which we know as science are the observation of facts, the inductions of laws or generalizations from the observed facts, and the verification of the facts, laws, and generalizations by experimentation. These three conditions of science are often subject to error through false or incomplete observation of facts, the induction of laws from too few or false facts, and the frequent human inability to reproduce natural phenomena, whereby experimentation may be done to confirm the laws or generalizations. In spite of these stringent demands of science in the establishment of truth man has been forced to live and think in terms of generalizations and laws, a fact which may be seen in the history of any of the natural sciences. Laws and generalizations have been the most prominent instruments of progressive thought.

In the field of medicine Julius Cohnheim, in 1877, expressed a generalization in the following words: "I believe that this process—referring to the embryonic development of the *monstra per excessum*, such as superfluous fingers, giant children, giant adults, giant extremities, etc.—is not confined to this field but also applies to a much wider and more important field, namely, the field of true neoplasms." By this generalization he meant that the neoplasms

and the *monstra per excessum* were probably due to some excess in the embryonic development of tissues. This is the generalization which stands out most prominently in the pathology of tumors, and is the one which is given preference in practically all modern text-books on the subject. Later Ribbert added to Cohnheim's prenatal hypothesis another one, which explained neoplasms by a postnatal cutting off of cells in scar-tissue.

The evidence which had been produced to establish or support the prenatal and postnatal rest hypotheses for the origin of tumors may be divided into three groups, *i. e.*, the facts relative to the occurrence and anatomic location of tumors, the published speculation relative to how they occurred, and experimental observations which were made as a result of the hypotheses.

The speculation has already been mentioned, and the anatomic observations may be briefly stated as follows:

1. Tumors do occur.
2. Some monstrosities, the duplex anatomic abnormalities, bilateral abnormalities, superfluous fingers, giant children, giant adults, elephantiasis of one or more extremities, inequality of growth in bilaterally symmetric organs, such as arms and legs, have an embryonic origin. Cohnheim says: "It is no mystical conception if we accept the embryonic anlagen as the cause of these excessive growths."
3. Some tumors occur in the localities of occasional developmental defects, such as the orifices of the nose, eyes, and lips and the tracheal bifurcation of the esophagus.
4. Nevi and moles occur usually as prenatal abnormalities.
5. Nevi and moles occasionally become malignant neoplasms.
6. As a result of segmentation of the fertilized ovum three distinct embryonic layers develop, out of which the specific tissues of the organism arise (Wolff, 1759; Meckel, 1812; Ponder, 1817; von Baer, 1829; Remak, 1851-1855).
7. The condition known as carcinoma is of epithelial or ectoblastic origin.
8. Sarcoma is of connective-tissue origin.
9. Tumors which contain tissues not normally found in the region in which the tumor developed occur; thus gland-like structures are found in gliomas of the brain, spinal cord, and retina. Gliomas with cystic areas which are lined by epithelium have been

seen in the fourth ventricle. Lipoleiomyomas of the kidney have been described. Striped muscle tumors in the uterus, vagina, kidney, and testicle are reported. Cartilaginous growths in the tonsils, neck, thyroid, breasts, testicles, kidneys, and bladder are mentioned. Teratomas in the vagina, uterus, kidneys, bladder, breast, parotid, and ovaries are rarely found. Glands are found in uterine myomas.

10. Tumors, such as ovarian neoplasms, nevi, lipomas, angiomas, myomas, and sarcomas of epiphyses are occasionally bilaterally symmetric; and exostoses, enchondromas, adenomatous polyps, and papillomas are sometimes multiple.

11. Tissues which are analogous to normal tissues are occasionally found in locations where they are not normally found. "Adrenal rests" have been described by Ribbert and others. Epithelial vestiges, known as Wolff-Gärtner ducts in the uterus and adnexa occur. Epithelial rests cut off in the scar tissue of ulcers and burns were emphasized by Ribbert and others.

12. Accessory organs, such as the thyroid, breast, pancreas, and spleen, are occasionally found.

These abnormalities lent circumstantial evidence in support of the speculative generalizations of Cohnheim and Ribbert. Although all these facts do not represent the basis of Cohnheim's generalizations, they do represent the most important and most often quoted facts in support of the rest hypothesis as popularized by Cohnheim, Ribbert, and their followers. Briefly, these may be analyzed in their relation to the hypotheses in the order in which they have just been mentioned.

No attempt is being made here, however, to disprove the circumstantial evidence which has been presented in support of the prenatal and postnatal hypotheses. The evidence herewith presented is simply circumstantial evidence, which has equal value in a negative or contradictory consideration of the hypotheses.

1. Tumors certainly occur, but all tumors are now known not to be alike, and many conditions which were considered under the heading of tumor when the Cohnheim-Ribbert hypothesis was formulated have been proved to be neoplasms which are due to infectious organisms which gain postnatal entrance into the body. Many, in fact most, of the carcinomatous and sarcomatous neo-

plasms are conditions which manifest themselves after or during chronic irritation. This is well exemplified in carcinoma in association with ulcers of the stomach, epitheliomas in association with irritation of the lip from smoking, and repeated or constant sunburns and sarcoma which follows injury, all of which and many more examples are strong evidence that some other factor plays a rôle in the development of such neoplasms. If the irritation happened to strike a spot in which there were already prenatal rests, then prenatal rests must be frequent enough to be found in the areas which are so frequently the seats of neoplasms.

As a matter of fact, literature and experience are strangely devoid of authentic examples of rests in the common seats of cancer. That the cells of cancer are derived from cells which are present is to be conceded, but that these cells must necessarily be cut off physically or functionally during embryonic or postnatal life seems unnecessary in the light of findings which appear in other parts of this paper.

2. Monstrosities occur, but many of these are the results of purely mechanical defects and are not neoplastic. Giant colons in some cases have been due to an absence of a portion of the bowel, an absence most likely due to the failure of the two embryonic portions of the bowel to unite during embryonic development. The tumor in such cases is not neoplastic in the sense that a carcinoma or sarcoma is neoplastic. In most cases they are merely distentions of the lumen of the bowel. Elephantiasis is frequently due to prenatal or postnatal mechanical obstruction to the returning lymph or blood supply. The condition is also composed of differentiated cells, and not partially or undifferentiated cells, which are characteristic of neoplasms.

Bilateral abnormalities, like the monstrosities, *possess completely differentiated tissues*, and do not consist of masses of *undifferentiated hyperplastic* cells, such as characterize carcinoma, sarcoma, and many benign neoplasms. Giant children and adults, while they certainly have their initiative in their own embryonic cells, are merely manifestations of the extremes of growth. They have a limit—the limit of differentiated tissues—and do not mani-

fest the unlimited growth of benign and especially malignant neoplasms. Variability of size in all living things occurs normally; there must be extremes. It is no more remarkable than the great variability of size of flowers on plants of the same species. They consist of normal tissues which are normally correlated and differentiated; their development is not detrimental to the symmetry or existence of the tissues or the whole organism, a distinction which is to be compared with the characteristic asymmetry and detrimentality of neoplasms.

3. Tumors do occur in localities of occasional developmental defects, but these are rare when compared with other conditions, such as carcinoma of the stomach, skin, prostate, and breast, in which organs developmental abnormalities have not been discovered with as great frequency as in such regions as the face.

4, 5. *Nevi* and moles are usually of prenatal origin, but when compared with the number of moles and *nevi* in existence, malignant *nevi* and moles are extremely rare. Indeed, the condition is rare when compared with other malignant conditions which do not arise in moles and *nevi* and have no apparent relation to any abnormality as an antecedent.

6. Carcinoma is conceded to be of epithelial, therefore ectoblastic, origin, but the cells of carcinoma and the cells of sarcoma are often morphologically indistinguishable and frequently bear no cytologic resemblance to the parenchyma of the tissues from which they are supposed to have grown.

7. Although sarcoma is supposed to be of mesoblastic origin, the cells are often morphologically indistinguishable from cells of epithelial or ectoblastic origin.

8. That tumors occur which contain tissues not normally found in the region in which the tumor grew is certainly true, but it has been demonstrated that the adenomatous or glandular tissues of an adenomyoma of the uterus have their origin directly from the endometrium of the uterus as diverticula. It may be suggested also that the much-quoted mixed tumor, namely, the glioma of the brain and cord which contains gland-like structures, is a condition in harmony with the fact that both central nervous tissues and

certain gland-tissues develop from the same stratum germinativum. Indeed, the variety of very different structures which are derived from the stratum germinativum of the ectoderm gives to that layer the possibility of producing many tissues; for example, in the same cyst of a breast one may find squamous cells, cuboid cells, and cells which are indistinguishable from sebaceous cells. It must not be forgotten that cells which normally produce columnar epithelium may produce squamous epithelium when those cells are placed in the position where squamous epithelium is demanded for protective purposes. It must be remembered also that within the compass of a single cell, namely, the fertilized ovum, all tissue possibilities exist. This clearly demonstrates the biologic fact that protoplasm is a plastic substance which readily adapts itself to abnormal environment. Conditions which are called "adrenal rests" in the kidney do occur, but nobody has actually demonstrated that such structures were really adrenal cells. Their analogy may be similar to the analogy which exists between cells of sarcoma and carcinoma, spindle-cell sarcoma, and epithelioma.

9. The bilateral symmetry of rare neoplasms, as bilateral fibromas, lipomas, and nevi, is in accord with the bilateral symmetry of many organs. Thus many bilateral axillary lipomas have been proved to be bilateral rudimentary or accessory breasts. The bilateral symmetry of the mammary gland does not especially predispose to bilateral carcinoma of the breast, although this condition does rarely occur. Bilateral ovarian simple cysts, cystadenomas and dermoids of the ovary occur, but the condition is more frequently single when found by the surgeons. Bilateral symmetry of fibromas of the nerves occurs, but there are some bilateral irritative conditions of nerves of known postnatal origin.

10. Accessory organs occur frequently, but neoplasms in such structures are rare as compared with the neoplasms which arise in structures which are not accessory.

11. Multiple tumors occur in many parts of the body, but here also they are associated with irritation which is also multiple or diffuse.

12. The so-called law of specificity of tissues from the three

embryonic layers is open to criticism of modern biologists, since it has been shown that in the regeneration of certain organs and tissues of some animals these tissues arise from different layers. The regenerated lens in the triton arises from a mesoblastic tissue in spite of the fact that the lens normally develops directly from the ectoblast. Muscles in the *Tubifex rivulorum* are regenerated from ectoblastic structures, although they are originally mesoblastic.

Hertwig says that the terms outer, inner, and middle germinal layers denote only the relative position of the cells which develop, at different times, and he reminds us quite appropriately that the entoderm and the mesoderm are both derived from the cells of the ectoderm. He further shows the incompleteness of our present knowledge of the germ layers by stating that it is still a question whether the chorda develops from the ectoderm, mesoderm, or entoderm in so simple an animal as the amphioxys.

Whether the middle layer is derived from the outer or inner layer, or both, is still an open question. As to the morphologic specificity of cells from these layers, it may be stated that many cells of moles are morphologically identical with connective-tissue cells, although they may be directly traced by continuity to the epithelium of the skin. Indeed, such cells are often indistinguishable from the cells of spindle-cell sarcoma and myoma, both of which are supposed to be of mesoblastic origin. Cells from an epithelioma (ectoblastic) of the skin are frequently morphologically indistinguishable from the cells of a sarcoma (mesoblastic).

The embryologists tell us that the epithelium of the kidney is of mesoblastic origin, and still many neoplasms of the kidney are morphologically carcinoma. From these facts it seems that the law of specificity of tissues has many exceptions and begins to lose its morphologic and functional specificity when studied from the standpoint of cytology.

The experimental evidence which was conducted by such authorities as Wilms, Lubarsch, Ribbert, Kaufman, Schweniger, Dooremal, Goldzieher, Garrè, Kaig, Jungengel, Goldmann, Mangoldt, Thiersch, Réverdin, Krause, Barth, A. Schmidt, Moller, Alessandri, Fütterer, Zahn, Leopold, Birch-Hirschfeld, Rosario

Traina, Bom, Traina, Nichols, Lecine and Legros, Roux and Barfurth, consisted of transplantations of embryonic and adult tissues into normal organs of animals of the same and different species and the artificial misplacement of cells and tissues in animals in their embryonic stage. In all cases in which the cells or tissues lived the cells remained or became differentiated into the cells of the normal tissues from which the injected or transplanted cells were taken. The transplanted tissues ceased to grow, and in no case was a typical neoplasm produced.

Lewin states, in summarizing these experiments: "Out of all of these experiments no atypical growths with progressive tendency to growth occurred. Teratomas occurred, but metastases did not occur. The growth showed a tendency to retrogress." Borst states: "There still remains much which is lacking and uncertain in the use of experiments which in other investigations have proved so advantageous. They have given no success in the field of tumor formation. At least, no one has been successful in producing experimentally a true blastoma. In general one may say that the histogenesis of tumors is a field of oncology which has not been sufficiently cleared up."

It may be seen that those of the profession who accept the prenatal or the postnatal rest hypothesis for the histogenesis of tumors do so from speculation and circumstantial evidence and not from observational or experimental proof.

In the brief space of time allotted for this paper the principles of the new conception of the development of neoplasms may be best illustrated by studying one organ, although similar facts have been demonstrated in several organs. In over 846 carcinomas of the mammary gland I have never seen the condition unless it was associated with a definite chronic mastitis. In over 1819 specimens of chronic mastitis I have found histologic pictures which present changes, without demarcation, to and including the picture of early carcinoma.

The normal breast is the direct outgrowth of the germinative or basal layer of the embryonic skin. The tubules and the acini possess two layers of cells, one consisting of differentiated or func-

tionating cells, the other a basal layer, the cells of which are difficult to distinguish in the normal resting or lactating breast, but which come into prominence only in chronic mastitis.

The function of the basal-cell layer of the skin is to reproduce the epidermis when this is destroyed. The same layer in the mammary acinus comes into prominence only when there is destruction of the functionating cells of the acinus. Its function is that of regeneration, a protective process. In acute or extensive destruction of the skin, including the basal layer, the defect is replaced by scar tissue. In acute or extensive destruction of the mammary acini the defect is also replaced by scar tissue. In chronic irritation of the skin there is an increased production of cells. In chronic irritation of the breast there is likewise an increased production of cells. In other words, there is an attempt to replace the normal functionating cells. Failure in the complete replacement of the differentiated cells is accompanied by an overgrowth of the cells of the germinal or basal layer. This condition has been termed by the writer secondary epithelial hyperplasia. The cells fill the lumen of the acinus and are morphologically identical with the cells of cancer, although none invade the stroma at this stage. From the fact that these cells are morphologically identical with cancer cells and that the only apparent line of demarcation between the condition and cancer consists of a migration of the cells into the stroma, it has been termed by the writer precarcinomatous condition.

Viewed from a biologic standpoint, there are certain processes which are visible in the conditions just described. Nature provides certain cells (germinative cells) the duties of which are to act as a reserve to reproduce the specific organic cells when the latter are destroyed. She provides that the process of regeneration be accompanied by overgrowth, a condition which is characteristic of all reproduction in most, if not all, forms of life. She further provides for the migration of living things when environmental conditions are not suitable for local existence.

The condition of migration in the case of cells has been described by the writer as tertiary or migratory hyperplasia. The

cells of carcinoma of the breast represent the biologic principle of migration of cells. The cells, as Hertwig has stated, have lost their organic or communistic function and have taken on their cytologic or individualistic function, the latter being to preserve their kind from annihilation.

It may be asked, how can a condition which will certainly destroy the whole organism be a protective principle? This perfectly natural question can be answered only by stating a general principle in biology, namely, that regenerative changes do not always consider the adaptation of the whole organism. Thus, scars which are regenerative after destruction often completely or partially incapacitate a limb and thereby are disadvantageous, often a detriment to the whole organism. It is a manifestation of a principle which is inherent in cells, cytologic life being primary and organic life secondary. Thus the planarian, a low form of multicellular organism, in response to certain stimuli, produces a new head when it already possesses one; the actinian produces a new mouth on the side of its body, under certain regenerative conditions, etc. Migration of animals not infrequently leads even to their complete destruction or to the destruction of other kinds of animals. Life exists at the expense of life, a fact which, like many other biologic facts, will doubtless never be understood until the ultimate purpose of life is known.

In review, it may be seen, from an examination of the literature, the best of which is herein quoted, that the prenatal and postnatal conception of the histogenesis of tumors is based upon a generalization for which there are no observations of facts relative to the actual development of neoplasms and no experimental proof which is in accord with the hypothetic conception, expressed in the prenatal and postnatal hypothesis of Remak, Durante, Cohnheim, Ribbert, and their followers.

It is a conception, formulated at a time when the term tumor embraced many apparently different pathologic conditions, some of which have since been shown to have definite postnatally acquired parasitic character and associations which have nothing to do with either prenatal or postnatal anatomic development of tissues other than that their normal special structure may form a

portal of entry or is in communication with some portal of entry, for a tissue destroying organism or irritant which causes a tissue reaction in the form of a neoplasm.

It was further an outgrowth of the so-called germ layer theory of embryologic development, a theory which, according to Hertwig, seems to leave out of account the biologic fact that the so-called germinal layers are but a few generations, perhaps even one generation, from each other, and that all these layers are but a few generations from the ectoblastic layer. Indeed, it is not absolutely settled whether the mesoblastic or middle layer is of ectoblastic or endoblastic origin. Some authorities consider it a direct derivative of both layers.

It is further based upon another theory, called the theory of specificity of tissues (Kölliker), which is open to criticism for the following reasons: In the regeneration of the muscles of the *Tubifex rivulorum* they are derived from the same cells which form the nervous system (ectoderm); in the *Tubifex rivulorum* the pharynx arises from distinct germ layers; the regeneration of the lens in the triton has its origin in mesodermic cells and not in ectoblastic cells.

Such a conception leaves out of consideration the most evident and essential characteristic of cells, namely, the power of reproduction or regeneration. It also leaves out the fact that the specificity of tissues consists of specific differentiation of cells, a condition which represents the final adult stages of cellular life and not the reproductive or plastic stages. Hair does not grow from hair, the nails do not grow from nails, squamous epithelium does not arise from squamous epithelium. These specific end products are the offspring of germinative cells which produce hair, nails, and epithelium by the individual power of differentiation of germinative cells, which occupy an absolutely essential and much overlooked position in the economy of an organism such as the human body.

CONCLUSIONS

1. The prenatal and postnatal theories of the development of neoplasms are based upon no observational or experimental evidence.

2. They were working hypotheses based upon anatomic locations which were identical with certain complicated embryologic developments and two theories, namely, the three-layer theory and the specificity of tissues theory, both of which are still open to criticism of modern biologists.

3. Certain facts prove that for certain organs such neoplasms as carcinoma and epithelioma are the direct descendants of cells which are normally present in those organs and which have a distinct normal postnatal function of regeneration.

4. Facts further prove that these generative cells take part in a local reaction which attempts to replace cells which have been destroyed by some chronic irritant.

5. Biologic facts prove that most if not all unicellular and multicellular organisms migrate to protect themselves from extermination, and that this regenerative activity is often irrespective of the welfare of the whole organ or organism.

6. The formation of neoplasms may be expressed as an attempted protective hyperplasia of germinative cells, a fact and not a theory.

7. This conception of neoplasms possesses three definite histologic pictures which may be described by three definite terms or expressions which require three distinct clinical and therapeutic procedures, and form a definite basis for a new classification of tumors, which will be presented in the near future.

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VII. A NEW CLASSIFICATION OF NEOPLASMS *

WILLIAM CARPENTER MACCARTY

I take the liberty of presenting a new classification of neoplasms† for the following reasons:

1. It has been clearly demonstrated that carcinoma in three different organs arises from the regenerative cells of the parenchyma of the organs, and not from the parenchyma of these organs (breast, skin, and prostate).¹

2. It has been definitely established that cancer-cells of different organs—even organs of different germinal layer origin—are often morphologically indistinguishable.²

* Read before the Section on Pathology, Amer. Med. Assoc., June, 1915.

† This brief statement of a biologic conception of neoplastic cytologic processes serves merely as a preliminary report, and is presented at the present time for the purpose of stimulating pathologists to study their early neoplasms and chronic inflammatory conditions in the light of the process of tissue regeneration. It also serves to point the way to the standardization of histologic and cytologic facts with clinical experience.

3. It has been definitely shown that even the best pathologists cannot always differentiate carcinoma from sarcoma, the cells being often morphologically indistinguishable.²

4. It may be seen from the writings of many authorities who classify tumors that their classifications are based on the histogenesis of tissues, and that many of these authorities express dissatisfaction with this basis of classification and apologetically accept it as the best, under the existing state of our knowledge.³

5. A review of embryologic facts relative to the histogenesis of the different tissues of the body clearly reveals a lack of definite information relative to the exact origin of many tissues, a fact which places any classification which is founded on the histogenesis of tissues on a theoretic basis.⁴

6. The histogenetic basis for a classification of tumors is also based on the theory of specificity of tissues which finds some contradiction in biologic experimental facts and in certain embryologic developmental facts.⁵

7. The classifications which are utilized today by the best authorities do not describe the condition of the cells of tumors, but merely name the tumors from the tissues from which they are supposed to, but probably do not, arise.³

The classification herewith presented is based on the following established biologic facts:

1. The cell is the recognized unit of life.
2. Tissues are communisms of specific or differentiated cells.
3. Organs are communisms of tissues.
4. The fertilized ovum, by a process of segmentation, produces cells which produce cells, which become differentiated into tissues.
5. During the process of the production of cells which produce tissues certain cells remain in a stage of reserve (regenerative cells) for the purpose of producing specific tissues when the specific tissues are destroyed.
6. In the presence of chronic irritation specific cells of tissues are destroyed, the reserve cells become hyperplastic, and sometimes, in the presence of failure to reproduce specific cells, they form an overgrowth, the cells of which sometimes migrate into the stroma.

7. The cytologic process of attempted regeneration expresses itself histologically in three definite stages or conditions: (a) By the presence of the atrophic or degenerating specific or differentiated cells, plus hypertrophic regenerative cells (primary cytoplasia); (b) by the absence of specific cells plus the presence of hypertrophic and hyperplastic regenerative cells (secondary cytoplasia), and (c) by the absence of specific cells plus the presence of hyperplastic regenerative cells plus migration of the hyperplastic regenerative cells into the stroma, lymphatics, neighboring and distant organs (tertiary or migratory cytoplasia) (Figs. 263-269).

8. The first cytoplasia (primary cytoplasia) represents a condition which is commonly accepted as a clinically benign condition. The third cytoplasia (tertiary or migratory cytoplasia) represents a condition which is commonly accepted as a malignant clinical condition. The second cytoplasia (secondary cytoplasia), with our present knowledge, is still doubtful as to malignancy or benignancy, and represents a group which has been variously considered by both pathologists and clinicians—a group which has caused endless confusion to the pathologist and clinician.

9. Biologically, certain regenerative cells react to irritation which destroys the end-products of their specific differentiation—first, by hypertrophy; second, by hyperplasia, and third, by migration.

The terminology of the classification which is herewith presented consists of well-known and accepted terms. It expresses, in its first word, the stage of cytologic activity in response to irritative stimuli; the second word denotes the tissue, the generative cells of which are involved in the neoplastic condition; the third word is merely a term which signifies condition of cells. Thus, by such an expression as primary fibrocytoplasia is meant that there is a condition of primary reaction of the regenerative cells of fibrous connective tissue.

In a primary reaction there is an attempted if not complete reproduction of the specific cells. In a secondary reaction there is a failure to reproduce specific cells, plus an overgrowth of generative cells. In the third reaction there is a migration of the hyperplastic generative cells. Each one of these cytoplasias is expressed by terms, the etymology of which is well known and accepted in biology:

Thus:

I. Primary (restauro-).....	{ fibro- myxo- lipo- leiomyo- rhabdomyo- epithelio- adeno- neuro- lympho- chondro- osteo- myelo- glio- endothelio- perithelio- melano- erythro- poly- x- }	} cytoplasia.
II. Secondary (expando-).....	{ fibro- myxo- lipo- leiomyo- rhabdomyo- epithelio- adeno- neuro- lympho- chondro- osteo- myelo- glio- endothelio- perithelio- melano- erythro- poly- x- }	} cytoplasia.
III. Tertiary (migro-).....	{ fibro- myxo- lipo- leiomyo- rhabdomyo- epithelio- adeno- neuro- lympho- chondro- osteo- myelo- glio- endothelio- perithelio- melano- melano- erythro- poly- x- }	} cytoplasia.

The term polycytoplasia is utilized to express a neoplastic condition in which all or many of the tissues are present, such as in teratomas and dermoid.

The term α -cytoplasia is the convenient term for grouping cytoplasia the tissue origin of which is unknown.

CONCLUSIONS

1. This classification, which is in accord with biologic terminology and conception, standardizes the science of neoplasia and allows complete correlation of clinical observation with cytologic activity.

2. It forms the basis of an accurate determination of the clinical value of pathologic data.

3. It will eventually expel the clinician's pessimistic idea of the work of the histopathologist, who, by means of his lack of standardization, has certainly incurred severe and detrimental criticism.

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VIII. THE EVOLUTION OF CANCER*

WILLIAM CARPENTER MACCARTY

Cancer is a migratory hyperplasia of the regenerative cells of tissues. This generalization has been formulated as a result of certain observations, and their correlation with biologic facts which are set forth in this paper. In order to portray a clear conception of these basic facts it will be necessary to state them somewhat in the order of their acquirement, and perhaps deviate at times for the sake of explanation.

In doing so, I desire to conform to the accepted principles of scientific thought and action. These consist of making of observations, deduction of generalizations and laws from observed facts, and the verification of the facts, generalizations, and laws by observation and experimentation.

During the years 1908-'09-'10, 764 specimens† containing mammary pathologic conditions came under the investigation. This material demanded classification, terminology, and clinical significance. What classification to adopt, what terminology to utilize, and what advice to give to the surgeon and clinician were not clear. The condition of our knowledge upon these subjects being chaotic, considerable time was devoted to an analysis of the teaching literature upon the mammary gland with definite objects in view. This analysis consisted of the accumulation of all the classifications which were available, record of the terminology which was being utilized by pathologists and clinicians, and the determination of the practical basis of clinical deductions.

The results have been previously published and therefore may be briefly stated. Almost every writer upon the subject of mammary pathologic conditions presents his own classification, which

* Read before The Brooklyn Pathological Society, November 11, 1915.

† The observations have since been confirmed upon over 2000 specimens of mammary conditions.

usually is not original, but is a modification of other classifications. The terms which have been utilized to express such conditions in American, English, German, and French literature amount to 142. Synonyms are numerous, and no writer has apparently published a complete list, a fact which in itself unfortunately has confused the working conceptions of pathologists and clinicians. All clinicians and pathologists, however, agree that certain frank carcinomas are malignant and demand radical operations. Practically all agree that it is unfortunate to remove chronic mastitis radically. But what is mastitis and what is carcinoma constitute the real problem which has puzzled both pathologist and clinician.

The term "precancerous" has arisen to express something which the writer has never seen histologically described and demonstrated twice alike. Many surgeons of very recent years call chronic mastitis "precancerous," and many benign conditions are doubtless being radically removed in the name of conservatism. Equally good authorities have been contradictory in their written opinions relative to what is histologically benign and what is malignant.

At this point it may be asked what have all these facts to do with the question of the evolution or histogenesis of cancer? Their relation consists simply in being the chaos which stimulated independent objective investigations of a large pathologic material.

Believing that the history of any organ is the history of its functional and structural units, attention was given to the mammary acinus, the object being the accumulation of detailed knowledge of what exists in and around this structure under normal and pathologic conditions.

In accordance with the first precept of scientific thought the following principal observations were made.

1. The acinus of the mammary gland, in its non-lactating condition, is a spheroid or ovoid blind end of a lacteal duct, and is lined by two layers of cells, the inner row consisting of so-called cuboid or columnar cells, and the outer row of flat, ovoid, or spheroid cells, which rest upon the connective tissue of the stroma. These have been found to be present under normal conditions, and also in association with chronic inflammation and cancer (Fig. 258).

2. During chronic inflammation of the breast some of the acini distinctly show exfoliation and necrosis of the cells of the inner row, and hypertrophy of the cells of the outer row. Sometimes the cells of the outer row are hyperplastic and fill the lumen, the cells of the inner row having completely disappeared. The hyperplastic cells of the outer row, when in this condition, frequently

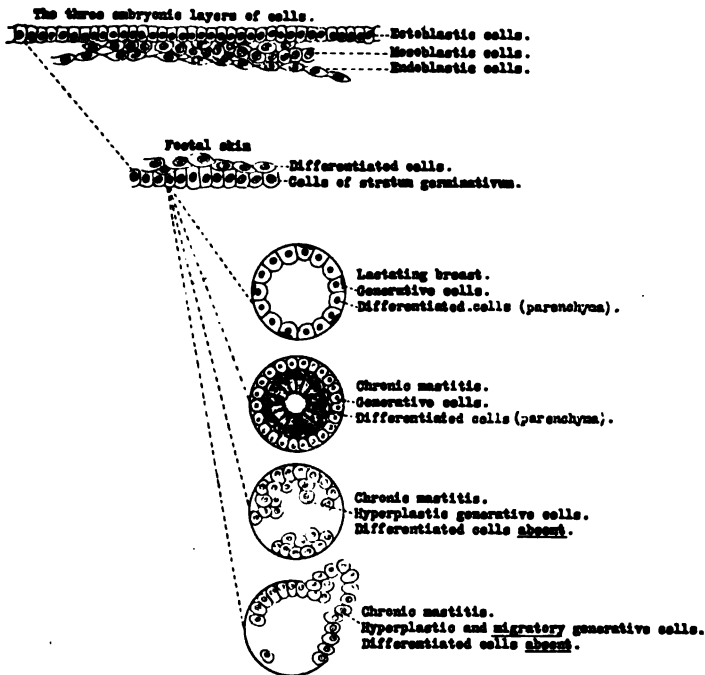


Fig. 263.—Showing the relation of the regenerating cells of the mammary acinus to the ectoblastic cells.

present morphologic characteristics which are indistinguishable from those of the cells of cancer.

3. In some acini in which there is an extensive hyperplasia of the outer row of cells the line of demarcation between the acinus and stroma is frequently confused, there being similar cells in the stroma (Fig. 263).

4. Acini which are described in observations 1, 2, and 3 are

found in either diffuse or encapsulated pathologic conditions in the breast.

These facts represent the fundamental observations which have been repeated many times, the conditions being found not only in different breasts, but also in the same microscopic field of the same breast.

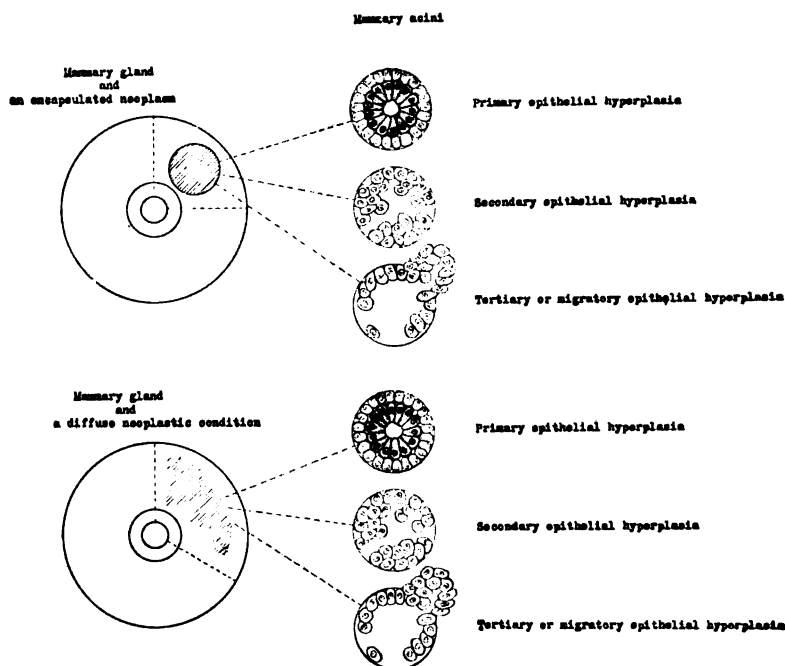


Fig. 264.—Encapsulated and diffuse fibro-epithelial neoplasia, showing the histologic pictures of primary, secondary, and tertiary (carcinoma) epithelial hyperplasia.

For the sake of record and description some sort of terminology for these conditions was necessary in the process of study. The simplest form of grouping being numeric, the conditions of the acini were termed primary, secondary, and tertiary hyperplasia respectively for observations 1, 2, and 3. Under these terms the conditions have been described by the writer repeatedly in the literature (Fig. 264). Further developments in the consideration of the conditions have seemed to indicate, however, a certain

incorrectness in the usage of the term hyperplasia for the condition which was called primary hyperplasia, since there is in reality no apparent hyperplasia, but simply hypertrophy. To be more scientifically correct, therefore, it has been deemed advisable to utilize the term cytoplasia, it being more accurately descriptive and more in accord with facts. One should merely state the condition of the cells in such objective studies. At present the conditions are spoken of as primary, secondary, and tertiary cytoplasia.

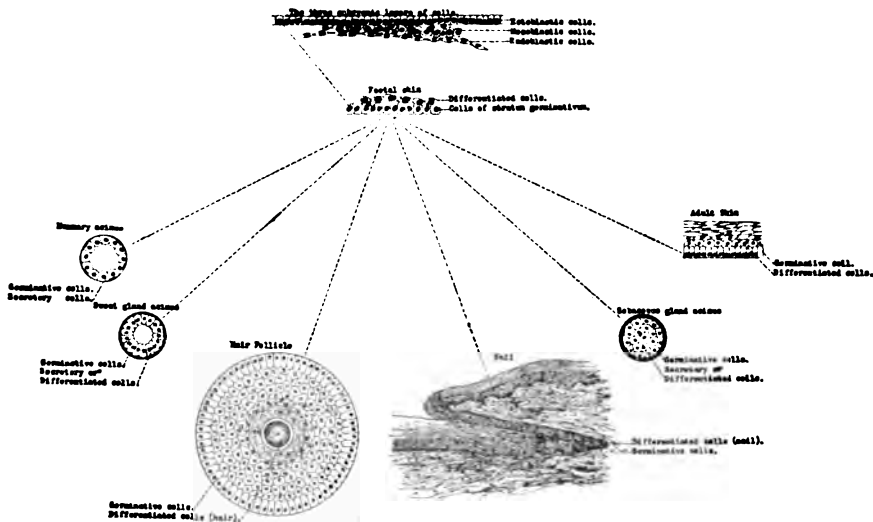


Fig. 265.—Organic differentiation of the ectoblastic cells. The ectoblastic cells become differentiated into the cells of the stratum germinativum of the embryonic skin. The cells of the stratum germinativum become further differentiated into the germinal cells of the mammary glands, sweat-glands, sebaceous glands, hair, nails, and epidermis. The germinal cells of these organs become further differentiated into the milk-producing cell of the breast, the sweat-producing cell of the sweat-gland, the fat-producing cell of the sebaceous gland, the hair of the skin, the nails of the skin, and the epidermis of the skin.

From these observations the deduction which has been made is that cancer cells of the breast are direct derivatives of the cells of the outer row in the acinus. With this deduction in mind the next step is the determination of just what the cells of the outer row are.

A review of works upon embryology by Keibel and Mall, Hertwig, Bonnet, Kollmann, Wimpfheimer, and others throws light upon

the biologic position of these cells. If one traces the life-history of the mammary epithelium (Fig. 263), one begins with the ectoderm of the three-layer stage of embryologic development. This layer of partially differentiated epithelium becomes more highly developed to form the so-called skin of the embryo. At first it is composed of one layer of low cuboid cells, which, with further development, becomes differentiated to form two or more layers of cells, the superficial layers differing from the first or basal layer in being flatter or less cuboid, with their long axes parallel with the surface of the body.

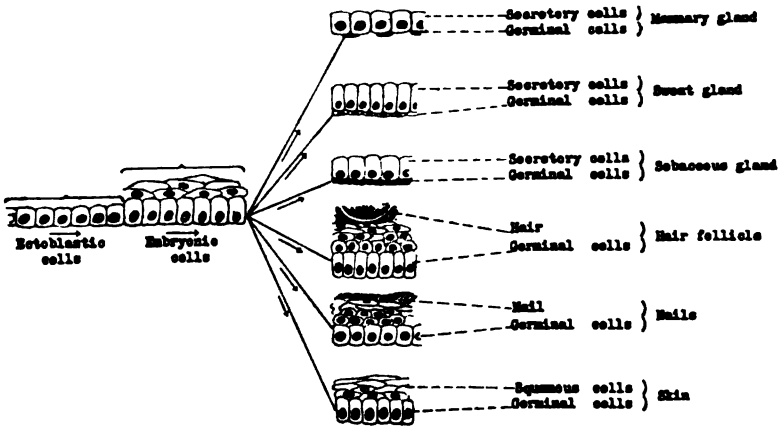


Fig. 266.—Cytologic differentiation of the ectoblastic cells. The ectoblastic cells become differentiated into the cells of the stratum germinativum of the embryonic skin. The cells of the stratum germinativum become further differentiated into the germinal cells of the mammary glands, sweat-glands, sebaceous glands, hair, nails, and epidermis. The germinal cells of these organs become further differentiated into the milk-producing cell of the breast, the sweat-producing cell of the sweat-gland, the fat-producing cell of the sebaceous gland, the hair of the skin, the nails of the skin, and the epidermis of the skin.

With both antenatal and postnatal development the superficial layers become more differentiated and less like their immediate predecessors, the basal layer, which, in this stage, the embryologists have termed the "stratum germinativum" of the skin or the germinating layer of the epidermis.

The history of the cells of this layer proves that they possess the power of divergence into several structural and functional derivatives. It may be spoken of as a plastic layer, at least in the

embryo. This expression of its broad functional and morphologic capacity is based on its behavior in the development of the appendages of the skin, namely, hair, nail, sweat-gland, sebaceous gland, and mammary gland (Figs. 265 and 266).

Histologic specimens which have been taken through embryonic skin and subcutaneous tissue in various portions show developmental activities of the stratum germinativum other than the production of epidermal cells. For example, in the development of hair-follicles the downward growth of the cells of the "stratum germinativum" into the subcutaneous tissue is accompanied by their differentiation into hair instead of epidermis. The examination of a fully developed hair-follicle, however, shows that there still remains a row of cells which corresponds to the "stratum germinativum" of the epidermis, and may be considered the stratum germinativum of the hair, the hair itself being formed by the differentiation of the basal cells. The sebaceous glands, nails, mammary glands, and sweat-glands possess their germinative strata, from which they are likewise formed by differentiation.

From this brief statement of embryologic facts one may construct a working diagram of the probable histogenetic position of the cells which form carcinoma. In the case of the mammary gland the cells of the inner row apparently are the differentiated, specific, and secretory cells, and the cells of the outer row correspond in relative position to the stratum germinativum of the skin and may logically be termed the stratum germinativum of the mammary parenchyma.

If these statements of observations be correct, the cancer-cell of the mammary gland is, biologically speaking, not only a direct descendant of the cells of the outer row, but is, thereby, the direct descendant of the germinative cells of the mammary secretory epithelium. This conclusion has aroused a biologic interest in this apparently important cell type as an independent and communistic unit of life. This cell, having been described as germinative or regenerative, the question of regeneration especially of epithelial cells became the object of investigation. The first and most studied field of regeneration in human pathology consists of repair

after acute injury, the second and less studied field consists of the natural repair coincident to what might be termed physiologic wear. The third and least studied field consists of the regeneration of tissues which are destroyed more rapidly than during physiologic wear, and not so rapidly as occurs in acute injury. In acute injury there is usually not only actual destruction of tissue, but also destruction of the regenerative or germinative cells of tissue. In this condition regeneration is not usually of the tissue which is destroyed, but a replacement of the defect by a supporting structure such as scar tissue. This may be illustrated by the experiment of complete destruction of the skin by scraping in which condition scar occurs. If the outer layers of the epidermis are scraped off, the basal (regenerative) cells remaining, regeneration occurs not in the form of filling a defect by scar tissue, but in reformation of the outer layers of epidermis from the basal cells. In physiologic regeneration the process of destruction is so gradual that it is scarcely recognizable.

It must be admitted that there are degrees of irritation and the effects of irritation; an irritant may destroy the differentiated cells, cease to act, and allow reformation from regenerative cells; a greater irritant may destroy the differentiated cells and continue to do so without the destruction of the regenerative cells. A still greater irritant, in so far as a single tissue is concerned, may destroy both differentiated cells and regenerative cells.

I believe it is fair, in the light of these facts, to assume that some kind of irritant, either in the mammary acinus or in the immediate stroma of the acinus, causes a degeneration of the parenchyma, because in the condition which is called chronic mastitis the parenchyma is frequently seen to be necrotic and exfoliated into the lumen, although the cells of the outer row remain intact. Associated with such a condition one also frequently finds both hypertrophy and hyperplasia of the outer row of cells. Such hyperplastic cells show mitotic figures and irregularities of size and shape coincident to karyokinesis. The cells themselves also are often distinguishable from the cells of carcinoma of the breast. This fact has led to a study of the morphology of cancer-cells, the

results being very surprising when considered in the light of morphologic qualities which have been thought to be so characteristic of cancer-cells.

During this study cells of cancer were examined in a fresh unfixed condition within from two to five minutes of the time their circulation was cut off. Under such circumstances there are cells which are almost perfect spheres, and possess a single spheric nucleus containing one or more spheric or oval nucleoli. There are many cells which are ovoids, and likewise contain perfect nuclei and nucleoli. In the same microscopic field one also finds spheric or oval planes of cells of different sizes, some without nuclei and nucleoli, some with nuclei and without nucleoli, and some with various sized nuclei and nucleoli.

In material which is perfectly fresh, and even in that which is not perfectly fresh, there are some perfect spheric and ovoid cells, these being apparently more common in perfectly fresh tissue, the dominating cells being really portions of cells or cells in which the outlines of the cell itself, the nucleus, and nucleoli, are distorted and indistinct. These qualities I believe are the results of an autolytic process which apparently occurs in many cells of neoplasms in the body, and very soon after the circulation of the tissue is cut off.

The close resemblance of apparently perfect cancer-cells, from different organs, to the cells which have been described in secondary cytoplasia of the same and different organs, has suggested the possibility that many of the morphologic irregularities of the cancer-cell which have been described are in reality artefacts which are due to autolysis and the cutting of the cell in various planes in the process of making thin sections. This seems plausible, since many cancer-cells are 20 micromillimeters in diameter, a condition which allows the same cells to be cut many times in the process of making thin serial sections. This would take place, however, in sections of any thickness, but the thinner the section, the fewer will be the number of perfect cells present. This is especially more likely to be true in the case of cancer-cells, because they are usually massed in contradistinction to the great regularity of arrangement of

normal tissue-cells. In a fresh unfixed condition the cytologic albumin is not coagulated—it retains its translucency and enables one to examine thicker sections, which, in my experience, have contained proportionately many more perfect cells than are found in fixed sections.

These observations have allowed the generalization that the cancer-cell and the intra-acinic hyperplastic cell of the germinative layer are practically always perfect cells with the characteristics of the component parts of a perfect cell, the variations which have been described being largely due to cytologic post-mortem autolysis, cytologic antemortem disintegration, natural variation in size and shape coincident to mitosis, and the fact that the cells are cut in various planes.

The difference between the intra-acinic cells of secondary cytoplasia which have not been considered to be cancer and unmistakable cancer-cells presents itself as the next problem. Since the difference, in my experience, is not one of morphology, it seems quite natural to direct attention to function, it being well known to cytologists that cells with apparently the same morphology may have different functions.

Briefly, one may simply state that the only apparent and as yet positively demonstrated difference between the cancer-cell and the cell of secondary cytoplasia consists of a difference in location, the one being intra-acinic and the other extra-acinic. The line of demarcation is, however, not so sharp as this might seem, because many acini may be seen in which there is merely a confusion of the line between acinus and stroma, the line itself having given way to the presence of the cells. One condition fades into the other. This change of location is known in biology as migration, a term which, in its biologic sense, does not infer individualistic motility. Whether or not these cells are motile remains to be proved. Regardless of the manner of migration the condition may be correctly spoken of as a migratory condition or a migratory cytoplasia of the regenerative cells.

The next important consideration in the analysis of the observations upon the genealogy of the cancer-cell is speculative, but is

speculative with the strong support of analogy to fundamental activities of living matter in general. As has been stated, observations show that regenerative cells of the mammary parenchyma are hypertrophic, hyperplastic, and migratory in the presence of a condition of the acinus which has long been considered to be chronic inflammation. It is well established that tissue-cells are derived by a process of differentiation of cells which do not possess the final qualities (functional or morphologic) of the tissue-cells which they produce. It is also well established that hypertrophy of the cell is one of the associates or manifestations of activity, and that hyperplasia means reproduction.

It is quite logical to assume also that hypertrophy, hyperplasia, and migration are aroused by stimuli which act upon the cell, and that in unicellular and multicellular life the most significant of cytologic functions is the protection of life itself, the three most important means of vital protection being alimentation, reproduction, and migration. These vital manifestations are so intimately interrelated that it is impossible to state which is the most important. Certainly extinction of kind would occur if these fundamental phenomena did not occur, and certainly there is no reason to believe that the cells of the human body differ in these fundamentals from the rest of life; moreover, all of these are too obviously present in the human organism to be discussed. In the light of these principles the regenerative cell, when stimulated by one or more of certain unknown stimuli, may be viewed. Under such abnormal environment the end-products of differentiation are prevented—the cell becomes hypertrophic in its effort to carry out its communistic function. In the presence of a slowly destructive agent it reproduces probably to protect its kind, and in the presence of continued abnormal environment it migrates. This seems to be a very simple biologic interpretation of histologic observations and their correlation with known biologic facts. This apparently protective cytologic activity, it is true, is destructive to the whole organism, but as a result of attempted regeneration this is not contrary to the activities of regeneration in other organisms, or even

the human organism, in which communistic welfare is not always considered.

Thus Morgan states, in writing upon this subject: "In certain cases of regeneration it can be shown that the result is entirely useless, or even injurious to the organism; hence the teleologic nature of the process is entirely lost sight of, and we are the more ready to accept a simple causal explanation of the phenomena. The best example of this that I can give is the development of a tail at the anterior end of a posterior piece of an earthworm. This process is not an occasional one, but is constant. An example of an apparently useful result, so far as the individual's well-being is concerned, but entirely useless from the point of view of the continuance of the species, is found in the development in the earthworm of a new head after the removal of the anterior end, including the reproductive region. New reproductive organs are not formed, and although, in virtue of the regeneration of a new head, the individual is capable of carrying on its existence, yet the race of earthworms is not thereby benefited. The production of two tails in lizards, or of two or more lenses in the eyes of newts, are examples of the regeneration of superfluous structures.

"If, however, it is claimed that in the large majority of cases the process of regeneration is for the welfare of the individual, and for the race also, this must be admitted, and it is this fact which has made a deep impression on the minds of many biologists."

He further states: "As Fischel (1900) has pointed out, the response is sometimes not adaptive, as when two lenses develop in the same eye in the salamander, and, we may add, as when an antenna develops in certain crustacea in place of an eye, or as when a tail develops instead of a head, or a head in place of a tail."

The deduction from the observations which have led to this discussion may be briefly summarized in a generalization; cancer-cells in the mammary gland evolve from the germinative or regenerative cells of the parenchyma of this organ, and probably represent a cytologic protective migratory hyperplasia which acts in accord with biologic laws which are often not compatible with communistic or organic life. This generalization has been

substantiated also by observations in the prostatic gland (Fig. 267), the hair-follicle (Fig. 268), skin (Fig. 269), lymph-gland,* blood* and stomach (Fig. 270). The relation which exists between these tissues and their germinative or regenerating cells in reaction to degrees of quality or quantity of irritation may represent a funda-

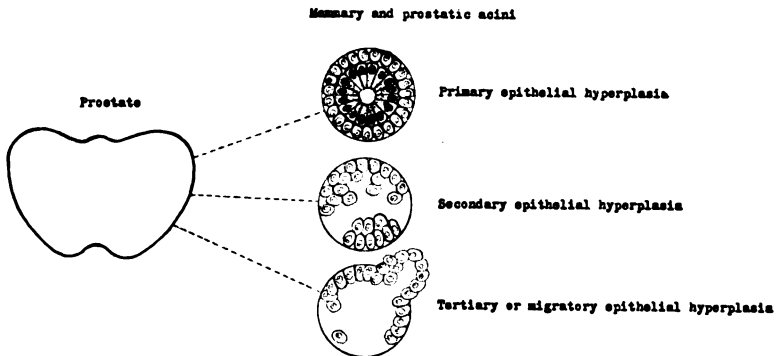


Fig. 267.—The prostatic epithelium presents the same arrangement of cells with the same cytologic characteristics which are found in the breast.

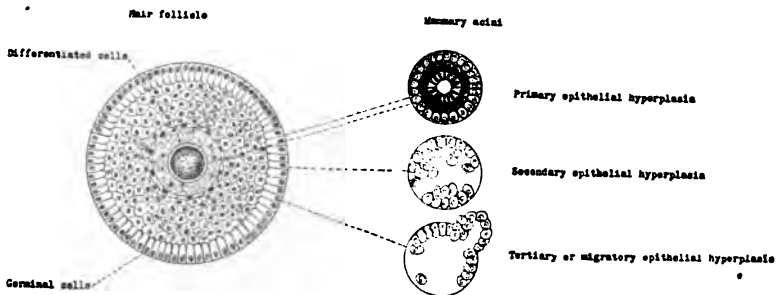


Fig. 268.—The principal cytologic changes which occur in the hair-follicle in chronic folliculitis are seen in the germinal cells, which present the same cytologic characteristics which are seen in the mammary acini when undergoing a condition of epithelial hyperplasia.

mental principle which will be applicable to all tissues. In view of this possibility, and as a stimulus to further investigations of regeneration of tissues in relation to neomorphosis, it may be well to group the tissues of the body and apply the same terminology to

* The work upon these organs has not been completed for publication.

the biologic position of these cells. If one traces the life-history of the mammary epithelium (Fig. 263), one begins with the ectoderm of the three-layer stage of embryologic development. This layer of partially differentiated epithelium becomes more highly developed to form the so-called skin of the embryo. At first it is composed of one layer of low cuboid cells, which, with further development, becomes differentiated to form two or more layers of cells, the superficial layers differing from the first or basal layer in being flatter or less cuboid, with their long axes parallel with the surface of the body.

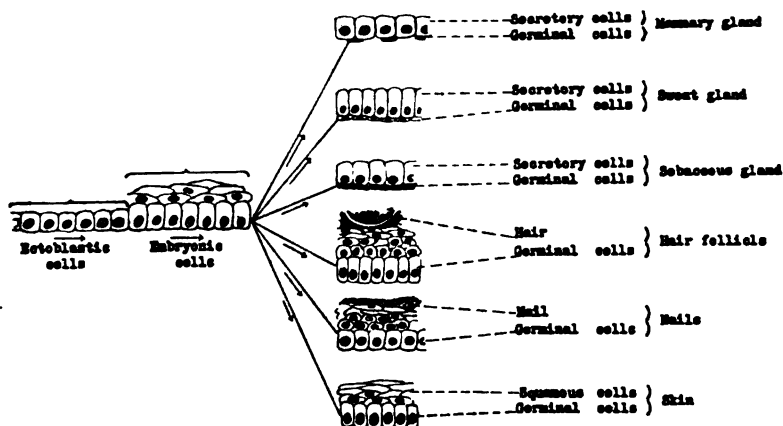


Fig. 266.—Cytologic differentiation of the ectoblastic cells. The ectoblastic cells become differentiated into the cells of the stratum germinativum of the embryonic skin. The cells of the stratum germinativum become further differentiated into the germinal cells of the mammary glands, sweat-glands, sebaceous glands, hair, nails, and epidermis. The germinal cells of these organs become further differentiated into the milk-producing cell of the breast, the sweat-producing cell of the sweat-gland, the fat-producing cell of the sebaceous gland, the hair of the skin, the nails of the skin, and the epidermis of the skin.

With both antenatal and postnatal development the superficial layers become more differentiated and less like their immediate predecessors, the basal layer, which, in this stage, the embryologists have termed the "stratum germinativum" of the skin or the germinating layer of the epidermis.

The history of the cells of this layer proves that they possess the power of divergence into several structural and functional derivatives. It may be spoken of as a plastic layer, at least in the

monly accepted as a clinically benign condition. The third condition is malignant, and second cytoplasia with our present knowledge is still doubtful as to malignancy or benignancy, and represents a group which has been variously considered by both pathologists and clinicians—a group which has caused endless confusion to the pathologist and clinician.

The terminology of the classification which is herewith presented consists of well-known and accepted terms. It expresses in its first word the stage of cytologic activity in response to irritative stimuli; the second word denotes the tissue, the generative cells of which are involved in the neoplastic condition; the third word is merely a term which signifies condition of cells. Thus by such an expression as primary fibrocytoplasia is meant that there is a condition of primary reaction to the regenerative cells of fibrous connective tissue.

In secondary fibrocytoplasia there is a hyperplasia of the fibroblasts, which are not differentiated into fibrous connective tissue, plus a localized absence of fibrous connective tissue.

In tertiary or migratory fibrocytoplasia there is an absence of fibrous connective tissue, plus a migration of the hyperplastic fibroblasts.

In a primary reaction there is an attempted if not complete reproduction of the specific cells. In a secondary reaction there is a failure to reproduce specific cells plus an overgrowth of regenerative cells. In the third reaction there is a migration of the hyperplastic regenerative cells.

This conception of the evolution of neoplasms standardizes the science of neoplasms and allows complete correlation of clinical observation with cytologic activity and forms the basis of an accurate determination of the clinical value of pathologic data.*

* See references, page 897.

IX. THE RELATION BETWEEN CHRONIC MASTITIS AND CARCINOMA OF THE BREAST *

WILLIAM CARPENTER MACCARTY AND EDMUND H. MENSING

Certain questions and their answers have evolved from a study of 967 mammary carcinomas and 406 simple chronic mastitides in the Mayo Clinic.

1. Is carcinoma always associated with chronic mastitis? By chronic mastitis is meant the presence of one or more of the following conditions: fibrosis, hyalinized fibrosis, lymphocytic infiltration; distortion, partial or complete destruction of the glandular groups; obliteration or dilatation of acinic lumina; atrophy, hypertrophy, or hyperplasia of the parenchyma. In this series of cases the association was constant.

2. Is chronic mastitis always associated with carcinoma? In our experience it certainly was not. There were 967 chronic mastitides with carcinoma and 406 simple chronic mastitides.

3. Are there any facts relative to a possible precancerous condition in chronic mastitis which point to a possible etiologic relationship between chronic mastitis and carcinoma? There are three distinct conditions of cellular activity in the parenchyma of the mammary acinus which bring chronic mastitis and mammary carcinoma into intimate association, and legitimately prohibit the consideration of the one condition without a consideration of the other.

In the mammary acinus, which is the structural and functional unit of the mammary gland, there are two rows of cells—an inner row, composed of cuboid or columnar cells, the long axes of which

* Read before the Southern Minnesota Medical Society, December 1, 1915. Reprinted from St. Paul Med. Jour., 1916, xviii.

are parallel to the radii of the acinus, and an outer row, the cells of which are oval or spheroid. The latter cells lie between the cuboid or columnar cells and the connective-tissue stroma, with their axes parallel to the circumference of the acinus. The prominence of the outer row varies considerably in different specimens, but it is invariably present in the condition of chronic mastitis.

In chronic mastitis the cells of the inner row are found frequently displaced toward the center of the acinus; they are frequently exfoliated and necrotic. In the presence of such a condition of exfoliation or displacement the cells of the outer row are hypertrophic and often hyperplastic. The cells of the inner row are occasionally absent, and the lumen of the acinus is seen to be filled with hyperplastic cells of the outer row. The latter cells present morphologic characteristics which make them indistinguishable from the cells of mammary carcinoma, although they are not present in the stroma.

The line of demarcation between the acinus and stroma is sometimes confused, thereby making it impossible accurately to state whether or not one is dealing with carcinoma (see appended literature).

The presence of two rows of cells, namely, the differentiated inner row and the undifferentiated or partially differentiated outer row, has been termed *primary epithelial cytoplasia*. The absence of the differentiated cells, plus the presence of hyperplastic undifferentiated or partially differentiated cells, has been termed *secondary epithelial cytoplasia*, and this condition, plus the invasion of the stroma by the hyperplastic cells, has been termed tertiary or *migratory epithelial cytoplasia*. We have, therefore, three distinct histologic pictures in chronic mastitis; the first is characteristic of all chronic mastitis, the second is characteristic of some specimens of chronic mastitis, and the third, in its early stages, is associated with the first and second condition. The third condition is the recognized picture of carcinoma; the first is a recognized benign condition, and, with our present knowledge, the clinical significance of the second condition is still undetermined, although it represents a precancerous histologic picture.

From these facts one may scientifically state that there is certainly an association of chronic mastitis with carcinoma, but one cannot scientifically state from these facts that chronic mastitis is the etiologic factor in mammary carcinoma. In fact, from an economic standpoint the immediate question for the practical clinician and surgeon is not one of etiology, but one of association. Prophylactic and therapeutic action can be scientifically taken without a knowledge of the specific etiologic factor. Such action may not be correct many years from now, but with our present knowledge it should be based upon what we now know of the clinical significance of the three easily recognizable histologic pictures which have been so constantly observed in a large series of specimens.

In comparison with these observations of pathologic association of the two conditions, certain clinical features may be of interest, although important clinical relational facts cannot be logically deduced. The average age of 962 patients with carcinomas was 47.9 years, in comparison to 40 years of 406 patients with cases of simple chronic mastitis. There is, therefore, a period of 7.9 years which may possibly represent the approximate period of development of a malignant process to the point of noticeability by the patient.

The presence of a discharge from the nipple in 8.4 per cent. of all carcinomas and 6.6 per cent. of all chronic mastitides is apparently significant only in paralleling the fact that all cases of carcinoma are associated with chronic mastitis.

Trauma as a possible etiologic factor in the development of chronic mastitis and cancer is greatly minimized in this series by the comparatively small percentage of patients in which this factor is recorded in the history. In cases of carcinoma of this series only 8.6 per cent. gave a history of trauma, while 4.4 per cent. with chronic mastitis gave a similar history. These percentages of trauma are doubtless filled with error, from the standpoint both of history taking and of history giving.

The fact that 13 per cent. of the patients with carcinoma and 22 per cent. with simple mastitis were unmarried, minimizes, to a certain degree, the possibility of lactation and its coincident infec-

tions having been an important rôle in the development of either chronic mastitis or carcinoma, and points to other sources of chronic inflammatory reaction in the gland.

The wide range of age at which both carcinoma and chronic mastitis occur, namely, seventeen years for both conditions, eighty-five years for carcinoma, and sixty-nine years for chronic mastitis, is significant from two standpoints. Clinically, a tumor in the breast can be malignant in spite of the fact that most mammary tumors in young women are benign. Pathologically, carcinoma is not a condition which is dependent on the age of tissues, but upon some other condition of tissues.

An analysis of the relation of clinical diagnosis to pathologic findings in this large series of cases reveals important facts. Of all the cases of chronic mastitis, 37.3 per cent. were diagnosed correctly by the clinician; the rest, or 62.7 per cent., depended on a fresh tissue laboratory diagnosis. These percentages are very high and somewhat surprising. They represent, however, a legitimate error of trained clinicians who must begin to realize that carcinoma starts as a microscopic condition which is not palpable and is not visible through the skin, and that at present there is no practical positive diagnostic method for early carcinoma. This legitimate clinical error is also evident in the clinician's inability to determine the pathologic condition of axillary lymphatic glands in carcinoma of the breast. In 325 of the cases there was a clinical diagnosis of glandular involvement.

Of these cases, only 120 (36.95 per cent.) proved to have actual carcinomatous glandular involvement. These errors emphasize the great value of immediate fresh tissue diagnosis in connection with operative interference. Practically one in every five of these patients may be saved from radical operation if the surgeon is accompanied in his work by a competent pathologist. From the facts which have been briefly presented there are five points to be borne in mind:

1. Carcinoma of the breast is always associated with chronic mastitis.
2. The percentage of legitimate error in the clinical diagnosis

of simple chronic mastitis and carcinoma is 62.7 per cent. and 23.9 per cent. respectively.

3. The percentage of legitimate error in the clinical diagnosis of the condition of the axillary glands is 36.9 per cent.

4. There are three distinct histologic pictures in chronic mastitis. At one extreme there is a benign condition, and at the other extreme there is a malignant condition. The means which may be easily recognized is at present doubtful.

5. The association of the two conditions is too close to allow a consideration of the one without the consideration of the other.

From a standpoint of advice from the surgical pathologist certain deductions may be drawn from these facts. The following plan, which suggests itself to the writers after an extensive experience with the pathologic conditions to be dealt with, and also an intimate association with the activities of surgeons, seems to be logical:

1. The conditions in the breast associated with classic clinical signs of carcinoma should be treated radically.

2. In doubtful cases in women near or over thirty-five years of age the entire mammary gland should be removed for immediate examination. If primary or secondary cytoplasia be present, nothing more should be done; if tertiary cytoplasia be present, a radical operation should be performed.

3. In doubtful patients near or under thirty-five years of age a wide sector of the mammary gland, including the pathologic conditions, should be removed for examination. If primary cytoplasia be present, nothing more should be done. If secondary cytoplasia be present, the rest of the mammary gland should be removed, and if tertiary cytoplasia be present, the radical operation should be accomplished.

This plan avoids incision of tumors. It removes the possibility of unnecessary radical operations and the consequent physical and psychic embarrassment. It provides for a scientific means of determining more accurately the stage at which cancer may be cured by surgical operations, and the extent of the operation which is necessary to effect such a cure.

For references see page 936.

X. MELANOEPITHELIOMA *

A Report of 70 Cases

ALBERT COMPTON BRODERS AND WILLIAM CARPENTER MACCARTY

The variety of synonyms which have been applied to pigmented malignant neoplasms indicates a lack of uniformity of opinion as to just what these tumors are histogenetically. They have been described as "melanosarcomas," "melanocarcinomas," "melanoblastomas," "melanomas," "melanoepitheliomas," "melanotic sarcomas" and "chromatophoromas." The majority of writers utilize the term "melanosarcoma," which has its basis of usage in the old classifications of neoplasms. These classifications were founded upon a theoretic conception of the specific origin of tissues in the three embryonic layers. The principal cells of nevi or moles, having been thought to have their origin in connective tissue of the skin, were, therefore, mesoblastic, and hence their neoplastic derivatives have been called sarcomas.

The conception that the spindle and oval cells which are characteristic of melanotic neoplasms of the skin are of connective-tissue origin is founded upon morphology, which we are rapidly learning is not an accurate criterion for the embryologic origin in any specific embryonic layer. Moreover, the direct continuity of the spindle and oval cells with the basal cells of the skin can be readily demonstrated not only in nevi (Fig. 271), but also in melanotic neoplasms (Figs. 272, 273, 274, and 275). The cells of the latter condition frequently assume an alveolar arrangement (Figs. 276, 277, and 278), which is very characteristic of epithelial tumors.

* Read before the Olmsted County Medical Society, December 9, 1915. Reprinted from Surg., Gyn. and Obst., 1916, xxii.

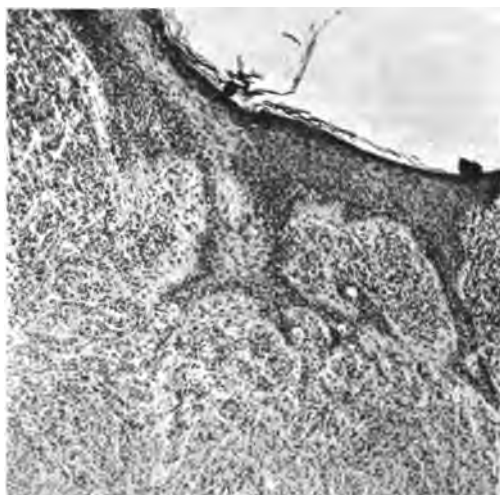


Fig. 271.—(A91,016.) A section of a mole showing the direct connection between the stratum germinativum and the subepithelial cells which are characteristic of moles.

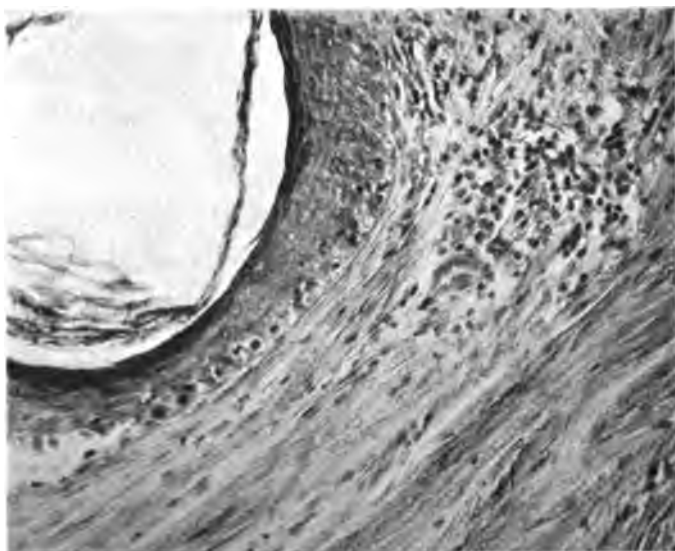


Fig. 272.—(80,193.) Photomicrographs showing hypertrophic and hyperplastic cells of the stratum germinativum of the skin over the left groin.

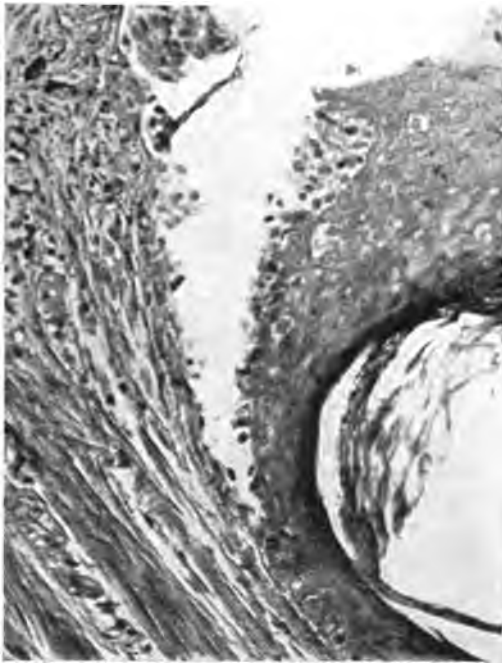


Fig. 273.—(80,193.) Photomicrographs of a portion of the same section (Fig. 272) showing a local hyperplasia with invasion by the cells of the stratum germinativum. The hypertrophic cells of the stratum germinativum are morphologically identical with the cells of the neoplasm.



Fig. 274.—(99,046.) Photomicrograph of an early migration of the malignant cells of the stratum germinativum in the skin of the right labium.

Such alveolar growths have been called "alveolar sarcomas" and "endotheliomas," the latter term inferring their origin in the lining of vessels. In the authors' experience, no evidence of vascular structure in connection with the alveolar arrangement has been demonstrable (Fig. 278).

We desire to utilize the term *melanoepithelioma* for the following reasons:



Fig. 275.—(80,195.) Photomicrograph of atypical melanoepithelioma arising in the germinal layer of the skin. The cells are in direct continuity with the stratum germinativum.

1. If the old three-layer hypothesis for the classification of tumors be adhered to, it may be well to remember that the pigment-bearing cells of the skin (Fig. 279), and perhaps the choroid (Fig. 280), both of which furnish the source of all the tumors of this series, have their origin in the ectoblastic layer, rather than the mesoblastic layer. There still seems to be, however, some doubt

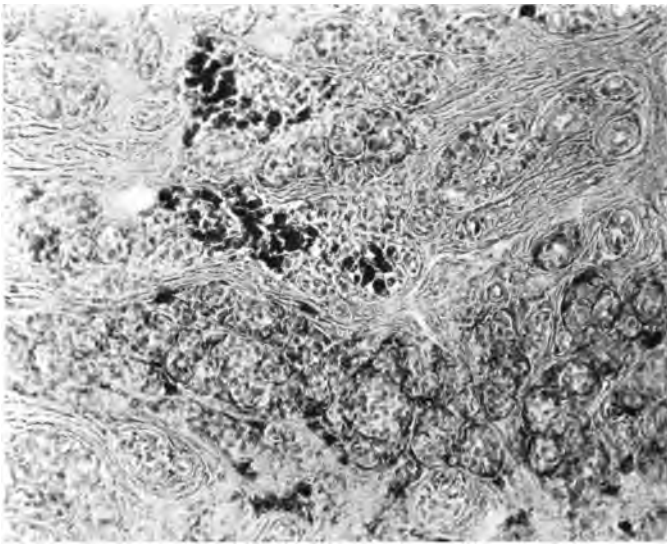


Fig. 276

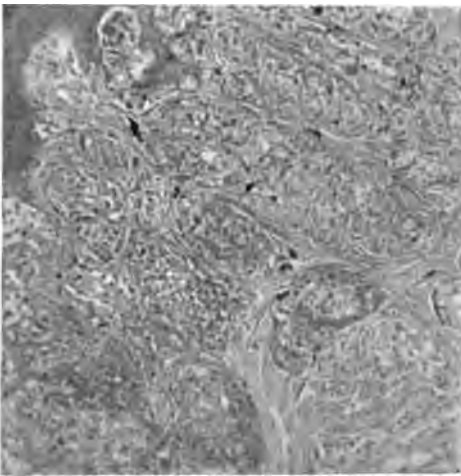


Fig. 277

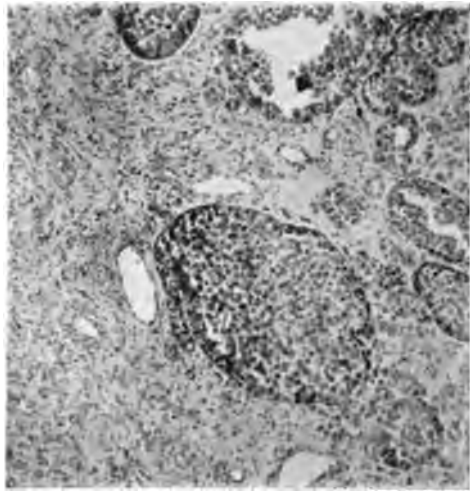


Fig. 278

Figs. 276, 277, 278.—(80,193, 80,193, 123,182.) Sections showing an alveolar arrangement of cells.

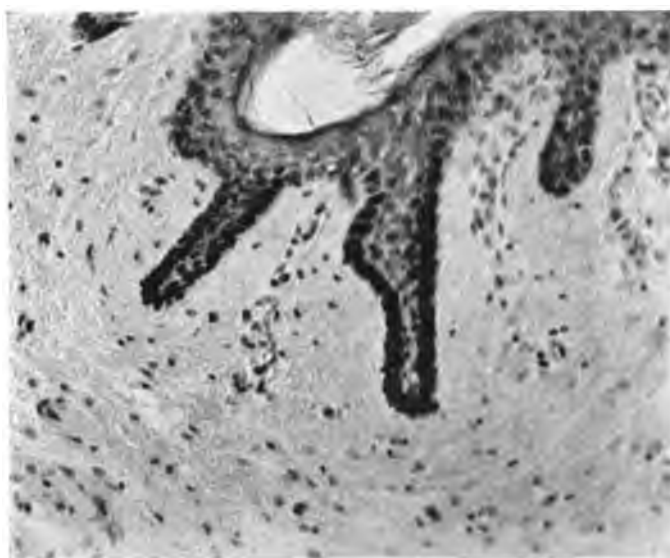


Fig. 279.—(A67.579.) Section through skin showing the normal location of pigment-cells.

as to the exact origin of the pigmented cells of the choroid, some authorities believing that they are a part of the embryonic optic bulb, and others considering them a part of the mesoblastic tissue which lies adjacent to the retina (Fig. 280).

2. The downward growths of spindle and oval cells of moles or nevi and melanotic neoplasms are in direct continuity with the stratum germinativum of the skin (Figs. 272, 273, 274, and 275).

3. The pigment-bearing cells of normal skin and of the downward growths of moles or nevi are in the basal layer (stratum

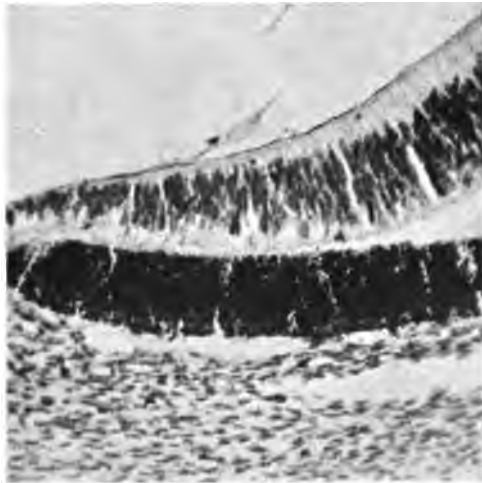


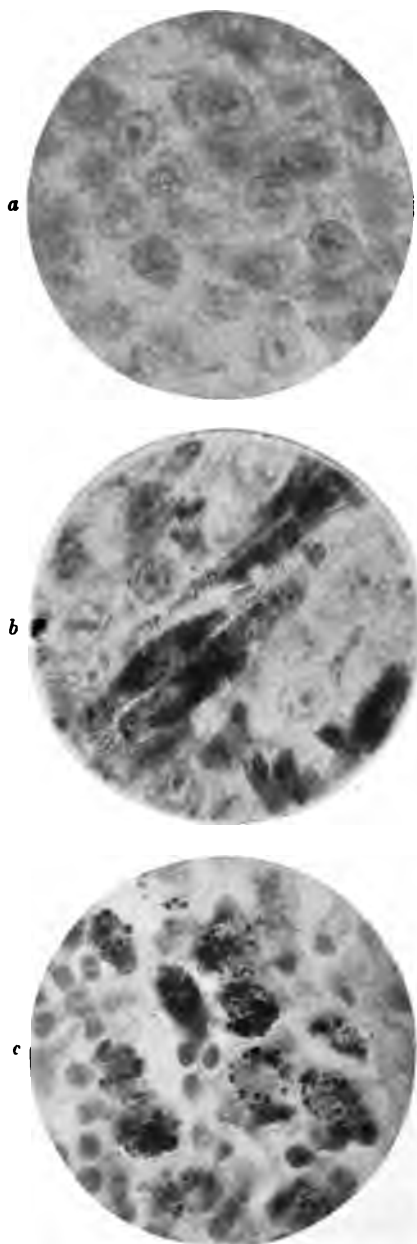
Fig. 280.—Section through an embryonic eye showing the relation of the choroid to the retina.

germinativum), and not in the subjacent connective tissue (Figs. 272, 273, and 274).

4. In accord with more recent observations of the histogenesis of epithelial neoplasms, they arise directly as a proliferation of the generative or regenerative cells of the parenchyma of organs, and not from either the differentiated cells or from "cell rests."

The cells of melanoepitheliomas may be oval (Fig. 281, *a*) or spindle (Fig. 281, *b*); all cells do not contain pigment (Fig. 281, *a*, *b*, *c*).

In our series of 70 cases the condition arose in both flat (Fig.



Figs. 281.—(105,603 and 36,641.) High (a, b, c) power photomicrographs showing variety of cells which are found in melanoepitheliomas.

282) and pedunculated (Fig. 283) pigmented areas of the skin. The local growth may be discovered when there is no apparent invasion of the tissue subjacent to the pigmented nevus (Fig. 284). In the majority of cases, however, there is extension to the subjacent



Fig. 282.—(57,193.) A flat pigmented mole upon the inner side of right leg, metastasis in the right inguinal glands; death within a year from operation.



Fig. 283.—(123,182.) An elevated, almost pedunculated, pigmented malignant neoplasm upon the left internal malleolus.

structures (Fig. 285). Pigment may occupy a large (Figs. 284 and 286) or small part of the tumors (Fig. 285).

The pathogenicity of this type of neoplasm may be seen to best advantage in the following tables:

1. Average age of patients, forty-nine years.	
2. Number patients between the ages of 20 and 30 years	7
" " " " " " 30 " 40 "	13
" " " " " " 40 " 50 "	14
" " " " " " 50 " 60 "	20
" " " " " " 60 " 70 "	8
" " " " " " 70 " 80 "	7
" " " " " " 80 " 90 "	1
Total	70
3. Oldest patient, eighty-four years; youngest, twenty-one years.	
4. Average duration of lesion before examination, eleven years.*	
5. Number of lesions which had their origin in birthmarks (nevi, warts, or moles)	35 (50 per cent).
Number of lesions which had their origin in miscellaneous pigmented areas, not typical moles	24
Number of lesions which had their origin in the eye	4
Number of lesions with origin unknown	7
6. Size of largest lesion was that of an orange.	
Size of smallest lesion was that of a pea.	
7. The following anatomic locations of original growths were noted:	
Scalp	1
Eye	4
Ear	2
Nose	1
Cheek	2
Jaw	5
Chin	1
Neck	1
Shoulder	3
Deltoid	1
Hand	2
Thumb	1
Breast	1
Chest	2
Back	3
Abdomen	1
Labium	2
Urethra	1
Groin	2
Hip	1
Thigh	2
Leg	8
Internal malleolus	1
Ankle	1
Heel	3
Foot	4
Toe	7
Not stated	7
Total	70

* This figure is only approximately correct, on account of the patient's inability to remember both the first appearance of moles and slight changes which take place in them.

8. Anatomic location of metastases	Regional lymphatic glands	36 cases
	General	10 "
	Liver	2 "
	Ovary	1 case
9. Number of patients with a history of previous operation		39
10. Number of specimens excised for diagnosis		21
11. Number of correct clinical diagnoses	41 (Out of 70 (58.6 per cent.) cases)	
" " doubtful " "	27 (Out of 70 (38.6 per cent.) ")	
" " incorrect " "	2 (Out of 70 (2.8 per cent.) ")	
12. The number of patients operated on between April, 1904, and January, 1915, that have been heard from directly or indirectly by letter		38
The mortality for patients operated on between April, 1904, and January, 1915, that have been heard from is 33, or 86.8 per cent.		
The number of patients dying within one year from last operation	24 (63.2%)	
" " " " " " two years " "	4 (10.5%)	
" " " " " " four " " "	1 (2.6%)	
" " " " " " eight " " "	1 (2.6%)	
Dead, date unknown	3 (7.9%)	
Total		33
The number of patients operated on between April, 1904, and January, 1915, that have been heard from and are living:		
1 year from last operation	2 (5.3 per cent.)	
2 years " " " "	1 (2.6 per cent.)	
3 " " " " "	2 (5.3 per cent.)	
Total		5 (13.2 per cent.)
Dead with metastasis at end of 1 year after operation		23
" " " " " " 2 years " "		4
" " " " " " 4 " " "		1
" " " " " " date unknown		1
Dead without demonstrable metastasis at last operation at end of 1 year		1
" " " " " " " " " " 8 years *		1
" " " " " " " " " " date unknown		2
" with " " " " " " " " 29 out of 33 (87.9 per cent.)		
First year deaths with demonstrable metastasis, 23 out of 24 (95.8 per cent.).		
Living with demonstrable metastasis at last operation at end of 1 year		1
" " " " " " " " " " 2 years		1
" without " " " " " " " " " 1 year		1
" " " " " " " " " " 3 years		2
Average duration of life after last operation, 11 months, 3 days.†		

The conclusions which may be drawn from the above-mentioned facts are:

1. The so-called "melanosarcoma" should be called properly a melanoepithelioma when such a condition arises in the skin or eye.

2. The condition arises as a migratory hyperplasia of the basal (regenerative or germinative) layer of the skin, and invades the sub-

* This case possessed a melanoepithelioma which had arisen in the choroid.

† This figure includes the eye case which lived eight years after operation.



Fig. 284.—(70,911.) Cross-section through a malignant pigmented hair mole upon the right cheek. The neoplasm has not extended visibly into the subcutaneous tissues.



Fig. 285.—(132,905.) Cross-section showing the extension of a growth from a pigmented mole into the subcutaneous tissue. The growth in the subcutaneous tissue lacks pigment; location, right leg just below the knee.

cutaneous tissues and distant organs as pigmented and non-pigmented oval, spheric, or spindle cells, all of which cells are frequently found in the same specimen or even in the same microscopic slide.

3. The evolution of such neoplasms in regenerative cells corresponds to the evolution of cancer in the skin, mammary gland, prostatic gland, and stomach.

4. The alveolar arrangement of cells in this series shows no evidence of any relation to vascular endothelium.



Fig. 286.—(143,701.) Metastatic growth of the left axillary glands.

5. The condition is one of middle life, although it may be found from childhood to old age.

6. An attempt at determination of the exact duration of the condition from its onset to a fatal termination has failed in this series.

7. There is no specific region of the skin which seems especially predisposed to the development of melanoepitheliomas unless it is on the lower extremities, which in this series form the greatest frequency of location.

8. *Nevi* certainly predispose to the development of the condition.

9. Metastasis is usually to the regional lymphatic glands.

10. From an economic or practical standpoint melanoepitheliomas which arise in the skin have a high mortality.

11. Melanoepitheliomas arising in the eye have a much better prognosis than those arising in the skin.

12. From a therapeutic standpoint the pathologic history of melanoepithelioma clearly points to the necessity of an early diagnosis and a radical removal of the primary lesion and regional lymphatic glands.

13. From a prophylactic standpoint pigmented areas of skin, such as warts and *nevi*, should be removed when these are in locations which are or have been subjected to injury.

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THE NECROPSY AS A PUBLIC SERVICE *

LOUIS B. WILSON

The very careful investigation of the subject of postmortem examinations in the United States, made two years ago by a committee of the New York Academy of Medicine,[†] showed that of the 17 large hospitals in the United States from which statistics were available for the years 1910, 1911, and 1912, the ratio of necropsies to deaths ranged from 7.3 to 62.7 per cent. In only 4 was the percentage above 25. As a reason for these very low percentages as compared with those of European hospitals, the committee states that "the main causes of the difficulties in obtaining permission for necropsies are due—(a) To the ignorance on the part of the public of the importance of necropsies to science, and therefore to the welfare of the people; (b) to the existing inadequate laws; (c) to the activity of undertakers and certain funeral societies; (d) to the inadequate rules of hospitals in this respect; and (e) to the claims of the department of anatomy."

While the foregoing are, no doubt, important deterring factors, I believe that much more important are—(a) The lack of genuine interest in postmortem examinations on the part of many physicians and surgeons, and (b) the lack of a commendably selfish interest in postmortems on the part of intelligent relatives of the dead.

Some physicians entirely lack an interest in necropsies because they are not interested in accurate vital statistics and in problems of heredity in disease, or because they do not appreciate the value

* Reprinted from *Jour. Amer. Med. Assoc.*, 1915, lxiv, 1560, 1562.

† "Report of Public Health, Hospital and Budget Committee, New York Acad. of Med.," *Jour. Amer. Med. Assoc.*, June 7, 1913, 1784.

of the necropsy in the correction of errors in diagnosis. Possibly some also hesitate to bring their diagnoses or operative procedures to the test of publicity in the necropsy.

Most intelligent laymen will respond to the argument that they ought to know the weaknesses of the members of their own families, but this argument is frequently omitted or greatly subordinated by the physician proposing that a necropsy be made. Usually necropsies are asked for as a favor to the physician, and rarely offered as a favor to the relatives.

The policy of the desirability of checking diagnoses and the results of operative procedures by the necropsy findings and of presenting to the relatives the desirability of their knowing the exact cause of death and the presence of intercurrent diseases has been followed out in the Mayo Clinic for many years. As a result, during the triennial period, 1910-1912, in 626 deaths, 512 necropsies were made, or 81.8 per cent.; in 1913 there were 269 deaths and 227 necropsies, or 84.4 per cent.; in 1914, 293 deaths and 258 necropsies, or 88 per cent., while to date (March 17th), in 1915, there have been 73 deaths with 73 necropsies, or 100 per cent.

Of the hospitals surveyed by the committee of the New York Academy of Medicine, which have patients of about the same social conditions as those in the Mayo Clinic, the two in America showing the highest percentage of necropsies to deaths are the Johns Hopkins Hospital of Baltimore and the Royal Victoria Hospital of Montreal. During 1910, 1911, and 1912, the former had 346 post-mortems, or 62.7 per cent. of its deaths, and the latter had 560 post-mortems, or 67.6 per cent. of its deaths.

NEED FOR NECROPSIES

At present our most accurate vital statistics concerning the cause of death from functional and chronic diseases are derived from the records of patients in charity hospitals. The charity patient, who for years has been examined and treated by physicians working in a public capacity before students, or at least using their knowledge for the teaching of students, as a rule, receives thorough scientific diagnosis and treatment; and, supplementing

this, the charity patient on whose body, in case of death, a necropsy is performed, is the subject of a death certificate which closely approximates the facts. But we must recognize that inferences drawn from statistics compiled from the records of great charity hospitals are apt to be more or less misleading when applied to specific cases in the estimation of family inheritance or life expectancy in the well-to-do. If Mendel's laws are of any value, forecasts of probable heredity can be accurately made only on a basis of accurately observed individual familial incidence.

In all those fields of investigation in which a knowledge of the exact cause of death is important the necropsy stands in first place. Aside from the infectious diseases and accidents, most of the fatal diseases of mankind can be diagnosed with accuracy only after death by an examination of the body both grossly and microscopically. This is particularly true of the three diseases chiefly resulting in the death of adults; namely, tuberculosis, cancer, and diseases presenting the cardiovascular renal syndrome.

In the consideration of facts in the family history, diagnosticians and life-insurance examiners will agree that often the cause of death as stated by the patient is absolutely untrustworthy, not because of wilful deception on his part, but because neither he nor his physician nor any one else really knows of what his ancestors died; and yet this is information which every intelligent man should have at hand. Every stock-breeder tries to know not only the cause of death, but also the intercurrent diseases of every one of his pure-bred animals that dies. In the same way nearly every intelligent man can be made to understand that he ought to know and has a right to know all the facts concerning the diseases of all the members of his family.

In the presentation of this argument to the intelligent layman, the obvious corollary is a frank admission on the part of the physician that he does not and cannot know everything about the diseases of every person, either by a clinical or a surgical examination. If quite honest, he must go further than this and acknowledge also that even after a postmortem examination he cannot approach absolute accuracy until microscopic examination of the

tissues has been made. He may say, however, in presenting the matter to the relatives, that his present knowledge from the clinical and perhaps surgical examinations goes about so far, that if he makes a careful postmortem examination he will probably be able to extend that knowledge considerably by the study of the gross specimens, and that if, in addition, he makes a microscopic examination he may extend it yet further, though he must honestly acknowledge that there are cases in which, even after every possible examination has been made, the truth may yet lie beyond his ken. It is also necessary to present frankly the fact that it is not alone the general cause of death which he seeks to determine, but also—what is sometimes of much greater interest to himself and the relatives—the incidental occurrence of abnormalities or other diseases. In making such acknowledgment of our shortcomings in the matter of clinical diagnosis, it may not be amiss to refer to the experience of many good clinics in regard to inaccuracies of clinical diagnoses as revealed at necropsy. Without going into this matter in detail, a general survey of the statistics furnished from a number of large hospitals where patients had been under examination for a long time before death seems to show that clinical diagnoses in carcinoma are correct in only about three-fourths of the cases, in tuberculosis in less than half of the cases, and in cardiovascular-renal diseases in less than 40 per cent. of the cases which come to necropsy. While it is not possible to raise the percentage of accuracy even by postmortem diagnoses to 100, yet such great improvement is possible by the necropsy method that its advantages are incontestable.

CONSENT FOR NECROPSY

The average layman may know that “modern progress of medical science and the proper development of medicine in the future are closely correlated with the use of the cadaver for postmortem examination,” but he is not therefore sufficiently interested to permit a postmortem on the body of his relative. The matter must appeal to him personally. Some men may be made to feel that they are under obligation to give the attending physician a chance

to review his antemortem observation. Some may be reached by the appeal that a postmortem study of the cases in which they are interested may immediately help in the diagnosis or treatment of other similar cases; but the one argument which appeals most to intelligent men is that they ought to know exactly, not only the cause of death, but also the incidental diseases of every member of their families. If we can get this point of view to be taken by the relative, his ignorance of the importance of the necropsy to science, the existence of inadequate laws and hospital rules, the objections of undertakers and burial societies, and the just cause of anatomists will all become as nothing and he will not only permit but will insist on a necropsy, and moreover, he will often demand a written report of the findings. It is to this commendable, intelligent self-interest that we should appeal in our arguments for necropsies. The most unyielding objections are based on mistaken religious scruples, yet even against these progress is possible and some of the clergy of the most conservative churches are now advising necropsies.

In relation to the details of presenting the subject of necropsy to the relatives of the deceased there are many important points which are sometimes overlooked. One of the long-established customs we long ago found it necessary to correct was that of having any one who chose to do so present the matter. We recognized that this must be done by one person only. It took more than a year in our clinic to change the customs of the institution so that the pathologist invariably should be called immediately on the death of a patient, and that he and he only should make any suggestions to the friends concerning the postmortem. It frequently happened in the early days that the good intention of sisters, nurses, surgeons, or clinicians in broaching the subject resulted in a very positive refusal. Formerly it was difficult to get the undertaker to wait until the necropsy was made before beginning his operations. This was overcome by conducting the necropsy as soon as consent had been obtained, at any hour of the day or night. Most important is the establishment of a reputation for honesty and frankness in reports to the relatives. At the first interview

the place and time for a formal report, after the necropsy and preliminary microscopic examination have been made, should be arranged for.

For a time consent was obtained only by the chief pathologist; then in later years by the first assistant in pathology. More recently the work has been turned over to the Senior Fellow in Pathology. This man must have been a graduate of a good medical school and have had one year in a general hospital before coming on service as a Fellow. He serves six months as junior, during which time he listens to his senior's requests for necropsies, but makes none himself except in emergencies. He then serves six months as a senior, during which time he makes requests. Of course, there is considerable difference in the personality of different men coming on this service, chosen as they are from all sections of the country and from different medical schools. The fact, however, that the necropsy service has not fallen below 80 per cent. in the last four years is sufficient evidence that it is not all a matter of personality, but more largely a matter of training in placing proper arguments before the relatives.

IN THE POSTMORTEM ROOM

As soon as possible after consent for a postmortem has been obtained the necropsy is made. This gives us a better knowledge of the condition of the body than is possible if a long delay has occurred. It gives better material for microscopic examination. It gives the undertaker a chance to do his work properly. The Senior Fellow is the chief operator at the necropsy; the Junior Fellow is his first assistant, and another Fellow in Pathology acts as clerk.

THE DEATH CERTIFICATE

The cause of death, as stated in the usual death certificate, is frequently inaccurate and often misleading. This is true in some instances even in which necropsies have been made. Many diseases, particularly the chronic infectious granulomas, neoplasms, and those involving the cardiovascular and renal organs, require microscopic evidence before a correct judgment can be formed of

the essential cause of death; but the death certificate must be signed before such a microscopic examination can be made. There is no provision for the correction of the original certificate after this further knowledge has been obtained. It would seem that in order to complete public records for statistical purposes a preliminary report might be made which should be sufficient on which to issue a burial permit, but the final record of the case should have added to it any data which were subsequently obtained by the pathologic examination of microscopic sections, chemical analyses, etc. Such records, if made by competent and careful observers, would greatly increase the value of our vital statistics.

GIVING INFORMATION TO RELATIVES

It is futile to expect laymen to be interested in or to give consent for necropsies on the bodies of their dead relatives unless they are told honestly, fully, and in simple language just what the findings are. If all pathologists would pursue this policy, not shrouding their work with mystery, but explaining everything in a perfectly matter-of-fact, business-like way, being careful to make themselves clearly understood and being willing to spend considerable time with the relatives in elucidating not only the actual findings, but also the possible meaning of these findings to the family of the deceased, the public would soon come to realize the desirability of having necropsies performed. Also, there would be implanted a wide-spread knowledge of means of safeguarding against certain forms of disease, for example, tuberculosis, syphilis, and cancer. Lessons mordanted in by grief sink deeply. We can do vastly more to spread a knowledge of disease in heart-to-heart talks with sorrowing relatives than we can by talking to the public in masses in lecture rooms when they would rather be at a moving-picture show. True, intelligent laymen, by reason largely of the campaign of education conducted by the American Medical Association and various boards of health, have already wide enough knowledge of cancer and tuberculosis so that the indolent physician may not with impunity "watch" such patients into the grave. It is to be hoped that the time will come when, similarly, laymen will have

INDEX OF CONTRIBUTORS

	PAGE
DONALD C. BALFOUR:	
Desmoid Tumors: Report of Two Cases in which the Tumor Occurred in the Operative Scars.....	655
A Device for Holding Solution Bottles in Operating Rooms.....	731
Foreign Bodies Swallowed by an Insane Woman.....	218
Non-strangulated Diaphragmatic Hernia Due to Indirect Injury.....	645
The Relative Merits of the Operations for Cancer of the Uterus.....	385
The Treatment by Heat of Advanced Cancer of the Cervix (Percy's Method).....	378
Varicose Veins.....	660
DONALD C. BALFOUR AND RUSSELL D. CARMAN:	
Gastrojejunal Ulcers—Their Roentgenologic and Surgical Aspects.....	156
EMIL H. BECKMAN:	
Correction of Depressed Fractures of the Nose by Transplant of Cartilage..	579
The Differential Diagnosis of Lesions of the Stomach and Duodenum ...	194
DAVID M. BERKMAN:	
Medical Treatment of Diabetics Preparatory to Surgical Treatment	476
WILLIAM F. BRAASCH:	
Perinephritic Abscesses.....	311
Significance of Vesical Symptoms in the Diagnosis of Renal Conditions. ...	320
WILLIAM F. BRAASCH AND ALEXANDER B. MOORE:	
Stones in the Ureter.....	327
ALBERT COMPTON BRODERS AND WILLIAM CARPENTER MACCARTY:	
XI. Melanoepithelioma: A Report of 70 Cases.....	923
RUSSELL D. CARMAN:	
Roentgen Diagnosis of Gastric Cancer, with Some Illustrative Cases	123
Roentgen Observation of the Gall-bladder and Hepatic Ducts after Per- foration into the Duodenum.....	247
The Roentgenologic Diagnosis of Duodenal Ulcer.....	220
RUSSELL D. CARMAN AND DONALD C. BALFOUR:	
Gastrojejunal Ulcers—Their Roentgenologic and Surgical Aspects.....	156
RUSSELL D. CARMAN AND ALBERT MILLER:	
The Roentgenologic Determination of Gastric Motility.....	96
EGERTON L. CRISPIN:	
Snuff-poisoning.....	854
Visceral Crises in Angioneurotic Edema.....	823
DELLA DRIPS AND FRANK C. MANN:	
The Relation of the Adrenals to the Pancreas.....	485

	PAGE
STELLA I. DUNLAP AND EDWARD C. ROSENOW: An Epidemic of Appendicitis and Parotitis, probably Due to Streptococci Contained in Dairy Products	282
LUIGI DURANTE: The Trophic Element in the Origin of Gastric Ulcer	70
Tuberculosis of the Tongue	3
GEORGE B. EUSTERMAN: The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers	174
CARL FISHER: Evisceration and Its Supposed Relation to Sympathetic Ophthalmia	573
HERBERT Z. GIFFIN: Diseases of the Spleen	511
III. Clinical Notes on Splenectomy	511
IV. Splenectomy for Splenic Anemia in Childhood and for the Splenic Anemia of Infancy	517
CHRISTOPHER GRAHAM: Notes on Gastric and Duodenal Ulcers	184
MELVIN S. HENDERSON: Operative Treatment of Bunions by the Mayo Method	705
Some Mechanical Derangements of the Knee-joint	681
Transplantation of Bone for Non-regeneration of the Tibial Shaft	701
IV. The Transplantation of Bone in Ununited Fractures of the Shaft of the Humerus	669
EDWARD STARR JUDD: Cirroid Aneurysm	561
Foreign Bodies in the Urinary Bladder	364
Subdiaphragmatic Abscess	298
EDWARD STARR JUDD AND JOHN D. PEMBERTON: Results of Operations for Exophthalmic Goiter	463
EDWARD C. KENDALL: The Isolation in Crystalline Form of the Compound Containing Iodin which Occurs in the Thyroid; Its Chemical Nature and Physiologic Activity	393
EDWARD C. KENDALL AND LOUIS B. WILSON: The Relationship of the Pathologic Histology and the Iodin Compounds of the Human Thyroid	422
WILLIAM CARPENTER MACCARTY: Studies in the Etiology of Cancer	885
VI. Facts Versus Speculation in the Professional Conception of Cancer . .	885
VII. A New Classification of Neoplasms	898
VIII. The Evolution of Cancer	903
WILLIAM CARPENTER MACCARTY AND ALBERT COMPTON BRODERS; X. Melanoepithelioma: A Report of 70 Cases	923

	PAGE
WILLIAM CARPENTER MACCARTY AND EDMUND H. MENSING:	
IX. The Relation Between Chronic Mastitis and Carcinoma of the Breast	918
FRANK C. MANN:	
Shock and Hemorrhage: An Experimental Study	739
A Study of the Gastric Ulcers Following Removal of the Adrenals	87
FRANK C. MANN AND DELLA DRIPS:	
The Relation of the Adrenals to the Pancreas	485
JAMES C. MASSON:	
Description of a Self-retaining Bladder Retractor	734
JUSTUS MATTHEWS:	
Studies in Surgery of the Tonsil	52
II. Tonsillectomy	52
CHARLES H. MAYO:	
Cholecystostomy Versus Cholecystectomy	256
Errors in Anatomic Development: Their Cause and Surgical Significance	865
The Examination, Preparation, and Care of Surgical Patients	869
Hydrocephalus, Spina Bifida, and Allied Diseases	551
Infection a Cause of Local and General Disease	879
Papillomas of the Gall-bladder	249
Repair of Small Vesicovaginal Fistulae	373
CHARLES H. MAYO AND HENRY S. PLUMMER:	
Goiter and Life Expectancy	456
WILLIAM J. MAYO:	
Acute Perforations in Abdomen—Traumatic, Spontaneous	292
Chronic Duodenal Ulcer	234
Gastric Ulcer	204
Procedures Following Nephrectomy	349
I. The Transperitoneal Closure of Duodenal Fistulas Following Nephrectomy	349
II. The Two-forceps Method for the Ligation of Vascular Pedicles, with Special Reference to Nephrectomy	355
III. The Management of the Ureter After Nephrectomy for Tuberculosis	361
The Relation of the Spleen to Certain Anemias	529
Restoration of the Bile-passage After Serious Injury to the Common or Hepatic Ducts	264
Surgical Considerations of Splenectomy	541
EDMUND H. MENSING AND WILLIAM CARPENTER MACCARTY:	
IX. The Relation Between Chronic Mastitis and Carcinoma of the Breast	918
HENRY W. MEYERDING:	
A Simple Operating Mallet	733
ALBERT MILLER AND RUSSELL D. CARMAN:	
The Roentgenologic Determination of Gastric Motility	96
ALEXANDER B. MOORE:	
Radiographic Diagnosis of Metastatic Pulmonary Malignancy: A Report of 71 Postive Cases	606

	PAGE
ALEXANDER B. MOORE AND WILLIAM F. BRAASCH:	
Stones in the Ureter.....	327
ROBERT D. MURSEY:	
Clinical Observations on Luetic Disease of the Heart and Aorta.....	846
GORDON B. NEW:	
Antrum Trocar and Irrigating Cannula.....	585
Bilateral Parotid Tumors.....	57
Fibrolipoma of the Larynx.....	587
Infections of the Mouth.....	19
GORDON B. NEW AND ARTHUR H. SANFORD:	
The Relation of Amebiasis to Pyorrhœa Alveolaris.....	25
SVERRE OPTEDAL AND EDWARD C. ROSENOW:	
The Etiology and Experimental Production of Herpes Zoster.....	779
JOHN D. PEMBERTON AND EDWARD STARR JUDD:	
Results of Operations for Exophthalmic Goiter.....	463
HENRY S. PLUMMER:	
Studies in Blood-pressure.....	448
I. Blood-pressure and Thyrotoxicosis.....	448
HENRY S. PLUMMER AND CHARLES H. MAYO:	
Goiter and Life Expectancy.....	456
ROY W. PORTEUS:	
The Nose and Throat in the Etiology of General Diseases.....	593
SAMUEL ROBINSON:	
Intratracheal Ether Anesthesia: A New Apparatus and Intratracheal Tube.....	715
The Treatment of Chronic Non-tuberculous Empyema.....	618
EDWARD C. ROSENOW:	
Elective Localization of Streptococci.....	764
Pathogenesis of Spontaneous and Experimental Appendicitis, Ulcer of the Stomach and Cholecystitis.....	276
EDWARD C. ROSENOW AND STELLA I. DUNLAP:	
An Epidemic of Appendicitis and Parotitis, probably Due to Streptococci Contained in Dairy Products.....	282
EDWARD C. ROSENOW AND SVERRE OPTEDAL:	
The Etiology and Experimental Production of Herpes Zoster.....	779
EDWARD C. ROSENOW AND ARTHUR H. SANFORD:	
The Bacteriology of Ulcer of the Stomach and Duodenum in Man.....	58
ARTHUR H. SANFORD AND GORDON B. NEW:	
The Relation of Amebiasis to Pyorrhœa Alveolaris.....	25
ARTHUR H. SANFORD AND EDWARD C. ROSENOW:	
The Bacteriology of Ulcer of the Stomach and Duodenum in Man.....	58
GILBERT J. THOMAS:	
Anuria for Five and One-half Days in a Patient on whom Left Nephrec- tomy had been done.....	346
Clinical Review of 240 Cases of Non-surgical Infection of the Kidneys and Ureters.....	336
Observations on the Clinical Prognosis of Syphilis.....	836

INDEX OF CONTRIBUTORS

951

LOUIS B. WILSON:

PAGE

The Necropsy as a Public Service.....	937
Pathologic Changes in the Muscular and Nervous Systems in Goiter....	438
Staining Sections of Living Tissue, Unfixed.....	722
Studies in the Pathology of the Spleen.....	500
II. Pathology of Spleens Removed for Certain Abnormal Conditions of the Blood	500

LOUIS B. WILSON AND EDWARD C. KENDALL:

The Relationship of the Pathologic Histology and the Iodin Compounds of the Human Thyroid.....	422
---	-----

BIBLIOGRAPHIC INDEX

- | | |
|---|---|
| <p> ACHARD, 780, 818
 Adami, 3, 17, 531, 897, 902
 Addis, 477, 484
 Albarran, 314
 Albee, 671, 680
 Albert, 8, 18
 Allen, 477, 478, 484, 485, 499
 Allessandri, 892
 Amyx, 373
 Apáthy, 723, 730
 Archibald, 600, 601, 605
 Aschoff, 206, 207, 217, 897, 902
 Ashby, 525, 528
 Avery, 777

 BABCOCK, 584, 662, 668
 Baer, 887
 Baetjer, 34, 35, 36, 103, 122
 Bainbridge, 897
 Baker, 602
 Balfour, 59, 156, 213, 215, 217, 218, 378, 385, 521, 645, 655, 660, 731
 Bang, 484
 Banti, 535, 539
 Barclay, 102, 121
 Bärensprung, 779, 821
 Barfurth, 893
 Barker, 709
 Barling, 520, 527
 Barnard, 301, 308
 Barrett, 20, 26, 30, 36
 Barsony, 158, 173
 Barth, 685, 699, 892
 Bass, 20, 26, 36
 Bassler, 99, 105, 121, 122
 Bateson, 867, 878
 Baum, 316, 319 </p> | <p> Baumann, 394, 421, 441
 Beaumont, 96, 121
 Beckman, 194, 247, 579, 652, 654
 Béclère, 158
 Beebe, 421
 Benedict, 483
 Bensley, 496, 499
 Berg, 172, 173
 Bergeim, 111, 122, 183
 Bergmann, 712
 Berkman, 476
 Bernays, 373, 374
 Bertrand, 483, 484
 Bethe, 723, 730
 Bevan, 59, 267, 275, 541, 548, 649
 Billings, 58, 69, 276, 281, 777, 778
 Billroth, 210
 Binger, 447
 Binnie, 645, 652, 653
 Birch-Hirschfeld, 892
 Bittorf, 782, 822
 Blackfan, 560
 Blackford, 212, 217
 Blancard, 3, 18
 Bland-Sutton, 519, 527
 Blaschke, 821
 Blaschko, 780
 Bloodgood, 758, 759, 762
 Boas, 98, 99
 Boeck, 779
 Boettcher, 84, 85
 Bolduan, 777
 Bolton, 58, 69, 95
 Bom, 893
 Bonnet, 897, 902, 907
 Borst, 893, 897, 902
 Braasch, 311, 319, 320, 326, 327, 335
 Braun, 25, 35 </p> |
|---|---|

- Brewer, 266, 275, 336, 345
 Brill, 535, 539
 Brinton, 236, 246
 Brissaud-Siccard, 780, 818
 Bristowe, 606, 617
 Broders, 434, 437, 923
 Brown, 777
 Brulé, 539
 Bruns, 565, 572, 671, 680, 712, 728
 Bull, 8, 18
 Bunting, 504
 Burghard, 519, 527
 Burmeister, 596, 605
 Burquoy, 5, 18
 Burrows, 828
 Butler, 578
 Byrne, 380, 384
- CABOT, 337, 345, 510, 537, 540
 Calamida, 592
 Calemida, 587
 Cameron, 421
 Campbell, 7, 18, 578, 780, 818, 821
 Cannon, 97, 115, 121, 122, 276, 280, 446, 447
 Carman, 96, 123, 156, 173, 179, 182, 183, 220, 247
 Carpenter, 525, 528
 Carr, 525, 528
 Caspary, 824, 834
 Catharine de Medici, 355
 Cauldwell, 420
 Celsus, 599
 Chappel, 18
 Chauffard, 534, 536, 539
 Chiari, 3, 17, 589
 Chvostek, 4, 18
 Cioffi, 87, 95
 Clarke, 5, 18
 Claus, 40, 51
 Cocks, 602, 603, 605
 Codman, 240, 246
 Coffey, 259, 274
 Cohnheim, 99, 886, 887, 888, 895, 897
 Cole, 42, 51, 103, 122, 220, 222, 772, 777
 Constantini, 7, 18
- Corner, 699, 700
 Cotton, 717
 Councilman, 897, 902
 Craig, 35
 Crile, 762
 Crispin, 645, 823, 854
 Crowe, 486, 499
 Cullen, 897
 Cuneo, 49, 51
 Cushing, 868, 878
 Czerny, 138, 155
- DALLA Vedova, 3, 7, 8, 18, 74, 85
 Dally, 9, 18
 Dandy, 554, 560
 Danlos, 7, 18
 Davis, 580, 597, 605, 777, 883
 Dawbarn, 566, 572
 Deaver, 595, 605
 Delamere, 49, 51
 Delavan, 4, 18
 Delbet, 662, 668
 Delorme, 632
 De Santi, 587, 590, 592
 D'Espine, 520, 527
 Dick, 596, 601, 605, 772, 777, 883
 Dodd, 111, 122, 178, 182
 Doflein, 25
 Dooremal, 892
 Dopfer, 780
 Draper, 335
 Drips, 485
 Drummond, 655
 Dunlap, 282
 Durante, 3, 70, 86, 87, 95, 445, 895
- ECCLES, 530, 539
 Edmunds, 499
 Ehrlich, 723, 730, 773, 777
 Einhorn, 100, 121
 Eiselsberg, 207, 208, 217
 Elliott, 88, 95, 520, 527, 530, 539
 Engman, 410, 420, 421
 Eppinger, 537, 540
 Epstein, 483, 484

Estlander, 630, 631
 Eusterman, 174
 Euteneuer, 18
 Euteneurer, 8
 Evans, 723, 730, 774, 777
 Ewald, 98, 99, 121
 Ewing, 751, 758, 759

FARR, 18
 Fenger, 403, 421
 Fernet, 782, 822
 Finch, 689, 690, 700
 Finzi, 87, 88, 95
 Fischel, 914
 Fischer, 3, 17, 195, 777
 Fisher, 47, 573
 Fitz, 483, 484
 Fletcher, 777
 Flexner, 773, 777
 Forssell, 212, 217
 Forssner, 776, 778
 Förster, 554, 560
 Fowler, 3, 17, 523, 524, 528, 632
 Francine, 236, 237, 246
 François-Dainville, 7, 18
 Frank, 18
 Fränkel, 238
 Franz, 378
 Freeman, 370, 372
 French, 520, 528
 Friedberg, 39, 51
 Friedenwald, 103, 122
 Friedman, 88, 95
 Fritz, 447
 Frost, 575, 576, 577
 Fürth, 421
 Fütterer, 206, 217, 892

GAREL, 587, 591, 592
 Garrè, 892
 Gaskell, 867, 869, 878
 Gatch, 756, 758, 759, 760, 761
 George, 104, 122
 Geraghty, 322, 326
 Gerber, 104, 122

Gershun, 18
 Gerster, 546, 548
 Ghose, 370, 372
 Gibelli, 87, 95
 Giffin, 500, 510, 511, 517, 535, 539, 649, 654
 Gifford, 573, 574, 575, 578
 Gignilleat, 282
 Gilfillan, 480, 484
 Godlee, 17
 Goebel, 587, 592
 Golbek, 591, 592
 Goldmann, 892
 Goldstein, 587, 589, 592
 Goldzieher, 892
 Gradle, 573, 577, 578
 Graefe, 473
 Graff, 523, 524, 528
 Graham, 124, 155, 174, 182, 184, 199, 276, 281, 777
 Graser, 360
 Grassi, 25
 Graves, 825, 834
 Greenwood, 573
 Gregory, 531, 539
 Gretsels, 522, 528
 Griffith, 828, 835
 Griffiths, 684, 699
 Groedel, 101, 102, 121
 Gros, 25, 36
 Gruber, 238
 Guthrie, 276, 281

HAHNEMANN, 880
 Haim, 282, 291
 Halstead, 829, 835
 Hamel, 3, 17
 Hamilton, 670, 680, 708, 897, 902
 Hanseemann, 8, 18
 Harmer, 111, 122, 178, 182
 Harrington, 828, 834
 Harrison, 370, 372
 Haudek, 106, 107, 114, 115, 116, 119, 122, 136
 Hawk, 111, 122, 183
 Hayem, 536, 540

- Hayes, 108, 122
 Head, 780, 818, 821
 Hecht, 868, 878
 Hedblom, 280
 Heichelheim, 99, 121
 Hektoen, 898, 902
 Hellstrom, 638
 Henderson, 669, 680, 681, 701, 705, 740, 758
 Henoeh, 824, 834
 Herb, 771, 777
 Hertwig, 553, 560, 892, 895, 896, 897, 902, 907
 Heuter, 708, 712
 Hewlett, 39, 51
 Heyerdale, 855, 858
 Hielscher, 854, 855, 857, 858
 Hilaire, 807, 878
 His, 870, 871
 Hiss, 531, 539
 Holbek, 592
 Holmes, 572, 712
 Holsknecht, 223
 Holt, 590, 592
 Holzknrecht, 107, 115, 116, 117, 122
 Homuth, 41, 51
 Hood, 282, 291
 Hopkins, 777
 Hoppe-Seyler, 777
 Howard, 781, 822
 Howell, 762, 771
 Hunt, 403, 421, 590, 592, 783, 822
 Hunter, 518, 527
 Huntington, 704
 Hutchinson, 394, 421, 527
 Hutchison, 517, 525
- INGALS, 587, 590, 592
 Irwin, 254
 Israel, 316, 319, 335
- JACOBI, 824, 834
 Jacobson, 266, 275
 Jaksch, 522, 528
 Janeway, 751, 758, 759
- Jefferson, 217, 241, 246
 Johns, 20, 26, 36
 Johnson, 39, 51, 858
 Jones, 560, 684, 685, 686, 688, 692, 699, 873, 878
 Joslin, 478, 484
 Judd, 59, 266, 275, 298, 312, 316, 319, 364, 463, 561, 588
 Jungengel, 892
- KAESTLE, 102, 121
 Kaig, 892
 Kanavel, 355, 363, 520, 527, 530, 539
 Kanëra, 782, 822
 Kaposi, 780
 Karewski, 477
 Kaufman, 892
 Keibel, 898, 902, 907
 Keith, 878
 Kemp, 98, 121
 Kendall, 393, 421, 422, 437, 441, 442, 447, 455
 Key, 173
 Kiyono, 723, 730
 Klemperer, 99, 121, 898
 Koch, 421
 Koenig, 685, 686, 699
 Kölliker, 896
 Kollmann, 871, 907
 Körte, 638
 Krause, 892
 Kretchner, 806
 Kümmell, 238, 246
 Küttner, 209
- LADD, 857, 858
 Lagomarsino, 18
 Lane, 686, 700
 LaRoque, 276, 281
 Laurens, 587, 592
 Lecine, 893
 Lee, 730
 Legros, 893
 Lemaire, 25, 35
 Lenhart, 421

- Lennander, 296, 828, 834
 Leoper, 780
 Leopold, 892
 Lesser, 780, 821
 Letulle, 40, 51
 Leube, 98
 Levy-Frankel, 7, 18
 Le Wald, 25, 35, 103, 115, 121
 Lewin, 893, 898
 Lewis, 217
 Lincoln, 356
 Lion, 158, 173
 Lippmann, 122, 223
 Lipsitz, 116, 122
 Lister, 880
 Litthauer, 276, 280
 Lockwood, 655
 Loeper, 818
 Lubarsch, 892
 Luce, 519, 527
 Lusk, 485, 499
 Lyon, 504, 510, 741, 758

 MacCARTY, 206, 212, 217, 254, 276, 281,
 885, 898, 902, 903, 918, 923
 Macewen, 580
 MacLachlan, 596, 605
 Madelung, 662, 668
 Magnus, 780, 822
 Mall, 869, 878, 898, 902, 907
 Mallory, 898, 902
 Mandelbaum, 535, 539
 Mangoldt, 892
 Mann, 34, 85, 87, 213, 259, 485, 739,
 758, 759, 760, 761, 762
 Mantle, 282, 291
 Marine, 421
 Marotta, 18
 Martin, 282, 291, 685, 699
 Masson, 734
 Matas, 561, 572
 Mathieu, 158, 173
 Matthews, 52, 603, 605
 Maxwell, 602
 Mayer, 723, 730

 Mayo (Charles H.), 59, 234, 249, 256,
 269, 275, 373, 420, 456, 551, 593, 605,
 661, 662, 668, 673, 680, 705, 712, 859,
 865, 879
 Mayo (William J.), 59, 198, 155, 156,
 173, 204, 217, 234, 246, 264, 275, 276,
 280, 292, 349, 363, 529, 541, 548, 649,
 828, 835
 Mayo-Robson, 156, 173, 235
 McArthur, 59, 270, 275
 McCrae, 17, 510, 617
 McDowell, 217
 McGrath, 281, 758
 McGuire, 645, 653
 McKenna, 59
 Meckel, 887
 Meltzer, 719, 762
 Mendel, 939
 Mensing, 918
 Metchnikoff, 883
 Meyerding, 733
 Meyjes, 587, 592
 Michaelis, 723, 730
 Mikulicz, 712
 Miller, 96, 173, 179, 183
 Milton, 825, 834
 Minkowski, 536, 540
 Mircoli, 7, 18
 Moller, 892
 Moon, 291, 777
 Moore, 327, 606, 872, 878
 Moreau, 158, 173
 Morgan, 553, 560, 898, 902, 914
 Morris, 828, 834, 835
 Morrison, 655
 Moynihan, 58, 69, 156, 158, 173, 205,
 206, 217, 235
 Much, 7, 18
 Mules, 573, 575, 576, 577
 Murphy, 671, 680
 Mussey, 846
 Myer, 121

 NANNINI, 18
 Neff, 568
 Neilson, 116, 122

- Nelson, 17
 Neubauer, 195
 Neveu, 25, 35
 New, 19, 21, 25, 37, 585, 587
 Nichols, 704, 893
 North, 777
- OCHSNER, 59, 664, 668
 Oftedal, 779, 821
 Oppenheim, 780, 818, 821
 Orde, 378
 Ormsby, 841
 Orr, 819, 922
 Osler, 510, 533, 539, 614, 617, 778, 823,
 824, 825, 828, 834
 Ostrowsky, 517, 525, 527
 Oswald, 394, 421
- PACKARD, 364, 372
 Paine, 883
 Paré, 355
 Pasteur, 880
 Paterson, 156, 173, 560
 Payr, 209
 Pearce, 777
 Pemberton, 463, 486, 487, 489, 499
 Pende, 87, 95
 Percy, 214, 378, 379, 380, 381, 383, 384,
 388, 389, 668
 Perthes, 209
 Pfeifer, 655
 Phemister, 704
 Phillips, 484, 476, 482
 Pierce, 729, 730
 Piersol, 510, 684, 699
 Plummer, 393, 410, 420, 421, 422, 429,
 434, 436, 437, 438, 439, 440, 447, 448,
 455, 456, 458, 459, 461, 462, 463
 Poirier, 49, 51
 Ponder, 887
 Pool, 524, 528
 Porter, 461, 760
 Porteus, 593
 Powers, 655
 Poynton, 883
- Prentiss, 870, 871, 873, 874
 Price, 26, 36
 Provera, 18
 Prowazek, 25, 29, 35
- QUINCKE, 825, 834
- RANSOHOFF, 632
 Recklinghausen, 552, 872
 Reed, 282, 286
 Rehfuß, 111, 122, 178, 183
 Reily, 780
 Reimann, 4, 18
 Remak, 887, 895
 Réverdin, 709, 892
 Ribbert, 887, 888, 892, 895, 898
 Richardson, 659
 Riche, 485, 499
 Ridlon, 696, 700
 Rieder, 101, 102, 121
 Riegel, 98
 Riesman, 477, 484, 898, 902
 Riggs, 828, 835
 Rimpler, 574
 Ringel, 638
 Risley, 476, 484
 Roberts, 370, 372
 Robinson, 618, 649, 654, 715
 Robson, 156, 173, 235
 Rodman, 212, 217
 Rohi, 780
 Röhmer, 195
 Rokitansky, 236, 246
 Rosenbaum, 782, 822
 Rosenberg, 782, 822
 Rosenow, 58, 59, 60, 69, 85, 86, 240, 246,
 252, 253, 255, 258, 276, 281, 282, 283,
 291, 341, 345, 386, 457, 533, 539, 596,
 600, 605, 764, 771, 777, 778, 779, 783,
 821, 822, 824, 834, 881, 882, 883
 Ross, 303, 308
 Rostouzew, 282, 291
 Rothschild, 614, 617
 Rothstein, 601, 605
 Roux, 893

- Rowan, 578
 Rowden, 158
 Rowe, 819, 822
 Ruck, 3, 17

 SACHS, 780, 822
 Sahli, 107
 Sajous, 421
 Salkowski, 195
 Sanford, 21, 25, 58, 86, 687
 Satterlee, 103, 115, 121
 Sattler, 779, 821
 Savignac, 158, 173
 Schauta, 378
 Schede, 631, 662, 668, 708, 712
 Schieck, 574, 576, 578
 Schirmer, 578
 Schliferowitsch, 4, 5, 7, 18
 Schmidt, 892
 Schottmüller, 817, 822
 Schrijver, 238, 246
 Schroetter, 591, 592
 Schulemann, 723, 730, 777
 Schulten, 638
 Schwarz, 421
 Schweniger, 892
 Seidell, 421
 Sellards, 34, 35, 36
 Senn, 863
 Sever, 560, 873, 878
 Shambaugh, 602, 605
 Sharpe, 553, 560
 Shattuck, 877, 878
 Shaw, 517, 527
 Sievers, 99, 121
 Simard, 40, 51
 Sippy, 178, 182
 Smith, 20, 26, 30, 36, 95, 434, 437, 604, 699, 777, 778
 Snellen, 574, 576, 578
 Somma, 522, 628
 Soresi, 156, 173
 Spemann, 869, 878
 Steinberg, 25
 Stellwag, 473
 Stewart, 336, 345

 Stieren, 377, 378
 Stockard, 869, 878
 Stohrs, 531
 Strauss, 99
 Strouse, 421
 Sudeck, 638
 Sullivan, 274, 275
 Summers, 354, 363
 Sunde, 781, 817, 822
 Sutherland, 519, 527, 578, 828
 Swarts, 741, 758
 Sweet, 336, 345, 485, 486, 487, 489, 499

 TATLOW, 156, 158, 173
 Teissier, 4, 18
 Tenney, 683, 699
 Thayer, 54
 Thiersch, 892
 Thomas, 336, 346, 836
 Tileston, 43, 51
 Tinker, 155
 Todd, 599, 605
 Traina, 893
 Trendelenburg, 662, 668
 Trevisanello, 781, 822
 Trimble, 7, 18
 Tsuda, 553, 560
 Turner, 520, 528

 ULRICH, 19

 VEDOVA, 3, 7, 8, 18, 74, 85
 Vetteson, 782, 822
 Virchow, 445, 614, 617, 698
 Voegtlin, 421
 von Baer, 887
 von Bürensprung, 779, 821
 von Bergmann, 712
 von Bruns, 671, 680, 712, 728
 von Eiselsberg, 207, 208, 217
 von Graefe, 473
 von Jaksch, 522, 528
 von Mikulicz, 712
 von Recklinghausen, 552, 872

- von Ruck, 3, 17
von Schroetter, 591, 592
Vuillet, 40, 51
- WAGNER, 824, 834
Wahle, 282, 291
Waldeyer, 594
Walton, 273, 275, 685, 699
Warfield, 606, 617
Warren, 548, 898, 902
Warthin, 50, 51
Wassermann, 836, 837, 839, 840, 843,
845, 846, 851, 853
Weber, 5, 18
Weir, 234, 246
Weis, 780
Welch, 246, 275
Weller, 528
Wells, 421
Welton, 575, 578
Wentworth, 517, 525, 527
Wertheim, 378, 386, 387
- White, 104, 122, 777
Whitelocke, 686, 699
Widal, 534, 536, 539, 780, 818
Wilkie, 181, 183, 238, 246
Willigk, 3, 17
Wilms, 629, 892
Wilson, 206, 207, 209, 217, 394, 420,
421, 422, 437, 438, 447, 455, 463, 500,
510, 521, 538, 540, 605, 722, 730, 875,
878, 937
Wimpfheimer, 907
Wislocki, 486, 499
Wolff, 522, 524, 525, 528, 887
Wood, 420, 596, 600, 605
Woodyatt, 777
Wulach, 102
Wyeth, 564, 572
Wyss, 779, 821
- ZAHN, 892
Ziegler, 898, 902
Zintsmaster, 4, 9, 18

INDEX OF SUBJECTS

ABDOMEN, gunshot wounds of, 292
 hemorrhage in, internal, symptoms of, 356
 pain in, 197, 198
 perforations in, acute, 292
 muscular rigidity in, 295, 296
 necessity of immediate operation, 292, 294
 symptoms of, 295
 spontaneous, 292
 traumatic, 292
 tenderness in, 197
Abdominal hysterectomy for cancer of uterus, 386
 lesions, differential diagnosis, 194
 pain in angioneurotic edema, 825
 wall, desmoid tumors of, 655
Abscess, alveolar, 19
 cold, of tongue, 6
 of kidney as cause of perinephritic abscess, 313
 perigastric, 299
 perinephritic, 311
 acute septic nephritis and, differentiation, 318
 bacteriologic examination of urine in diagnosis of, 316
 classification of, 311
 cortical abscess as cause, 313
 diagnosis of, 316
 differential diagnosis, 318
 etiology of, 312
 nephrolithiasis as cause, 313
 phenolsulphonephthalein test in diagnosis of, 317
 primary, 311
 pyelogram in diagnosis of, 317
 pyonephrosis as cause, 312

Abscess, perinephritic renal, functional test in diagnosis of, 317
 tuberculosis as cause, 312
 results after operation, 318
 rupture of kidney as cause, 314
 secondary, 311
 subdiaphragmatic abscess and, differentiation, 318
 traumatic perinephritis as cause, 314
 treatment of, 318
 urinalysis in diagnosis of, 316
 without renal involvement, 315
 x-rays in diagnosis of, 317
perisplenic, 299
peritonsillar, 599
subdiaphragmatic, 298
 associated with appendicitis, 303, 304
 with gall-bladder operations, 305
 with perforating gastric ulcers, 306
 with peritonitis, 301, 306
 with ruptured duodenum, 305
 gall-bladder, 306
 with tuberculous lesion elsewhere in abdomen, 307
 diagnosis of, 304
 drainage in, 307
 duration of, 304
 etiology of, 300
 following focal infection, 307
 operation on stomach, 306
 perinephritic abscess and, differentiation, 318
 prognosis of, 308
 symptoms of, 303
 treatment of, 307

- Abscess, subphrenic, 298. See also
 Abscess, subdiaphragmatic.
 Acinus of mammary gland, 904
 Adenitis, cervical, relation of tonsils to,
 600
 Adenoids, large, in adult, 603
 Adhesions in splenectomy, 541
 Adrenal rests, 888, 891
 Adrenalectomy, flow of pancreatic
 juice after, 486
 gross anatomic changes after, 486
 histologic changes in pancreas after,
 496
 ulcers of stomach following, 87
 Adrenals, relation of, to pancreas,
 485
 removal of, flow of pancreatic juice
 after, 486
 gross anatomic changes after, 486
 histologic changes in pancreas
 after, 496
 ulcers of stomach following, 87
 Albee's inlay bone graft in ununited
 fractures of shaft of humerus, 671
 Alimentary canal, 1
 Allen's treatment of diabetes, 478
 Alpha iodine, 441
 Alveolar abscess, 19
 sarcoma, 926
 Amebæ in mouth, 25, 29
 Amebiasis, relation of, to pyorrhœa
 alveolaris, 25
 Amœba buccalis, 25
 dentalis, 25
 gingivalis, 25
 kartulisi, 25
 oralis hominis, 25
 Amyx's operation for small vesicovag-
 inal fistula, 373
 Anæmia pseudoleukæmica infantum,
 splenectomy in, 522
 Anatomic development, errors in, 865
 cause and surgical significance,
 865
 Anemia, hemolytic, pathology of spleen
 in, 506
 splenectomy in, 513
 Anemia, pernicious, pathology of spleen
 in, 504-506
 relation of spleen to, 537
 splenectomy in, 512, 537
 relation of spleen to, 529
 splenic, in childhood, adult form,
 splenectomy for, 518
 splenectomy for, 517
 in infancy, splenectomy for, 522
 pathology of spleen in, 500-504
 relation of spleen to, 535
 splenectomy in, 512, 535
 Anencephalia, 552
 Anesthesia, intratracheal ether, 715
 indications, 715
 new apparatus and tube, 715
 technic of intubation, 718
 vaporizing apparatus, 721
 Aneurysm, cirroid, 561
 classification of, 562
 clinical history, 562
 etiology of, 562
 ligation of common carotid artery
 for, 565
 treatment of, 563
 Wyeth's treatment, 564
 of aorta in syphilis, blood-pressure,
 850
 physical findings, 849
 symptoms, 847
 treatment, 851
 Angine herpetique, 782
 Angioneurotic dermatoses, 825
 edema, abdominal pain in, 825
 visceral crises in, 823
 Animals, gall-bladder in, 259
 Antrum trocar and irrigating cannula,
 585
 Anuria in patient with one kidney, 346
 Aorta, aneurysm of, in syphilis, blood-
 pressure, 850
 physical findings, 849
 symptoms, 847
 treatment, 851
 disease of, in syphilis, 846
 blood-pressure, 850
 physical findings, 849

- Aorta, disease of, in syphilis, symptoms, 847, 848
treatment, 851
- Appendicitis, epidemic of, 282
experimental, pathogenesis of, 276
spontaneous, pathogenesis of, 276
subphrenic abscess associated with, 303, 304
- Appendix, vermiform, perforation of, 294
- Area medullovasculosa, 552, 872
- Arterial tumors, cirroid, 561
- Artery, cystic, location of, 266
splenic, as preliminary step in splenectomy, 546
- Arthritis, relation of tonsils to, 597, 600
- BACILLUS** tuberculosis in tuberculosis of tongue, 7
- Bacteria in thyroid gland, 457
in tonsils, 596
- Bacteriologic examination in non-surgical infection of kidneys and ureters, 340
of urine in diagnosis of perinephritic abscess, 316
- Bacteriology of gastroduodenal ulcer, 58
- Balfour's treatment of ulcer of stomach, 213
- Bang's method of determining percentage of blood-sugar, 483
- Barker's operation for bunion, 709
- Beck's paste in chronic empyema, 627
- Bertrand's method of determining percentage of blood-sugar, 483
- Bevan's incision for exposing gall-bladder, 267
for operations on gall-bladder and biliary passages, 541
- Bilateral parotid tumors, 37
associated with lymphatic leukemia, 42
diagnosis, 49
due to local infection, 47
recurrent, 37
- Bilateral parotid tumors, syphilitic, 39
treatment, 50
tuberculous, 40
- Bile in production of ulcers of stomach, 94
rate of formation, 259
- Bile-duct, common, injury to, restoration of bile-passage after, 264
obstructed portion, division of, with forceps, 270
excision of, with end-to-end union, 268
union of, to duodenum, by rubber tube, 274
direct, 272, 274
two-row suture anastomosis, 273
- Bile-passage, restoration of, after injury to common or hepatic ducts, 264
- Biliary passages, operations on, Bevan's incision for, 541
- Bismuth and vaselin in chronic empyema, 627
- Bladder, foreign bodies in, 364
neurosis of, 323
perforations of, 296
retractor, self-retaining, 734
- Blood, abnormal conditions of, pathology of spleens in, 500
relation of spleen to, 533
- Blood-pressure and thyrotoxicosis, 448
in goiter, 448
in hyperplastic goiter, 452
in non-hyperplastic goiter, 452
in snuff-poisoning, 855
in syphilitic disease of heart and aorta, 850
studies in, 448
- Blood-sugar, determining percentage, 482
- Boas and Ewald's test-breakfast, 98
- Boas and Strauss' modification of Riegel's test-dinner, 99
- Bodies, loose, in knee-joint, effect of, 686
indications for operation, 687
method of production, 684

- Bodies, loose, in knee-joint, operative technic, 692
symptoms, 687
- Bone, transplantation of, for non-regeneration of tibial shaft, 701
in ununited fractures of shaft of humerus, 669
- Bottles, solution, device for holding, in operating rooms, 731
- Breast, acinus of, 904
cancer of, chronic mastitis and, relation between, 918
trauma as etiologic factor, 920
cancer-cell of, 909
- Bridges, ill-fitting, infections about, 20
- Bronchitis, relation of tonsils to, 599
- Bulbar deformity as sign of duodenal ulcer, 220
- Bunion, anatomic findings in, 705
Barker's operation for, 709
definition of, 705
Heuter's operation for, 708
Mayo's (Charles H.) operation for, 705
after-care, 711
technic, 710
operations for, 708
Reverdin's operation for, 709
Schede's operation for, 708
- CALCULUS, renal, as cause of perinephritic abscess, 313
diagnosis of, significance of vesical symptoms, 323
ureteral, 327
diagnosis of, sources of error, 332
hematuria in, 329
localization of, 333, 335
pain in, localization of, 327
palpation of, 330
sources of error in diagnosis, 332
treatment of, 331
urinalysis in, 329
vesical irritability in, 329
x-rays in diagnosis, 332
- Cancer, etiology of, studies in, 885
- Cancer, evolution of, 903
of breast, chronic mastitis and, relation between, 918
trauma as etiologic factor, 920
of cervix, heat in treatment of, 378, 388
Percy's treatment, 378, 388
two-stage operation for, 388
of duodenum, diagnosis, 198
of pyloric end of stomach, ulcer and, differentiation, 209
of stomach, diagnosis, 201
inoperability, evidences of, 138
symptoms, 201
x-rays in diagnosis of, 123, 202
alteration of pyloric function, 130
altered motility, 132
size and capacity of stomach, 133
carcinomatous ulcer, 137
displacement of stomach, 134
early cancer, 139
filling defects, 125
fungous type, 135
gaping of pylorus, 131
interpreting signs, 141
latent cancer, 139
lessened flexibility, 133
mobility, 133
mucoid type, 137
operability, 137
peristalsis, 131
pyloric obstruction, 131
scirrhous type, 136
- of thyroid, 458
- of uterus, abdominal hysterectomy for, 386
inoperable, treatment of, 389
operations for, relative merits, 385
vaginal hysterectomy for, 387
Wertheim's operation for, 386
- Cancer-cell of mammary gland, 909
- Cancerous ulcer of tongue, tuberculous ulcer of tongue and, differentiation, 9

- Cannula, antrum irrigating, 585
- Carcinomatous change in ulcer of stomach, 206
- Cardiac lesions in goiter, 443
- Carotid arteries, common, ligation of, for cirroid aneurysm, 565
- Cartilage, transplantation of, for depressed fractures of nose, 579
 - technic of operation, 581
- Cartilages, semilunar, 683
 - injuries of, indications for operation, 687
 - method of production, 684
 - symptoms, 687
- Catarrhal gall-bladder, 250
- Cautery in treatment of ulcer of stomach, 213
- Cell, cancer-, of mammary gland, 909
- Cells, germinative, 894
 - lymphoid, of tonsils, 595
- Cephalocele, 552
- Cervical adenitis, relation of tonsils to, 600
- Cervix, cancer of, heat in treatment of, 378, 388
 - Percy's treatment, 378, 388
 - two-stage operation for, 388
- Chemical constituents of thyroid, 395
- Cholecystectomy and cholecystostomy, relative mortality, 262
 - tumors of stump of cystic duct after, 267
 - versus cholecystostomy, 256
- Cholecystitis, causes of, 251
 - drainage of gall-bladder in, 261
 - pathogenesis of, 276
- Cholecystostomy and cholecystectomy, relative mortality, 262
 - versus cholecystectomy, 256
- Chorea, relation of tonsils to, 600
- Chromatophoroma, 923
- Circulation, disturbed, in production of ulcer of stomach, 72
- Cirrhosis of liver, relation of spleen to, 531
 - splenectomy in, 514, 532
- Cirroid aneurysm, 561
 - classification, 562
 - clinical history, 562
 - etiology, 562
 - ligation of common carotid artery for, 565
 - treatment, 563
 - Wyeth's treatment, 564
- Clinicopathologic conference, 944
- Club-foot in spina bifida occulta, treatment, 560
- Cohnheim's hypothesis for origin of tumors, 886
- Cold abscess of tongue, 6
- Colic, renal, occurring with herpes zoster, 782
- Common bile-duct, injury to, restoration of bile-passage after, 264
 - obstructed portion, divulsion of, with forceps, 270
 - excision of, with end-to-end union, 268
 - union of, to duodenum, by rubber tube, 274
 - to duodenum, direct, 272, 274
 - two-row suture anastomosis, 273
- Copenhagen heart, 857
 - snuff, poisoning from, 854
- Cough in malignant metastases in lungs, 611
- Cretinism, 456
 - thyroid feeding in, 456
- Crises, visceral, in angioneurotic edema, 823
- Crowns, ill-fitting, infections about, 20
- Crucial ligaments, 683
- Cystic artery, location of, 266
 - duct, stump of, tumors of, after cholecystectomy, 267
- Cystitis in non-surgical infection of kidneys and ureters, 339
 - pyelonephritis as cause, 321
 - renal infection as cause, 323
- Cystoscopic diagnosis of non-surgical infection of kidneys and ureters, 338

- Cysts of lung, metastatic pulmonary malignancy and, x-rays in differentiation, 615
- Cytoplasia, epithelial, migratory, 900, 919
 primary, 900, 907, 916, 919
 secondary, 900, 907, 917, 919
 tertiary, 900, 919
- DAIRY products, streptococci in, epidemic of appendicitis and parotitis probably due to, 282
- Decortication operation for chronic empyema, 632
- Deformity, bulbar, as sign of duodenal ulcer, 220
- Delorme-Fowler operation for chronic empyema, 632
- Dermatoses, angioneurotic, 825
- Dermoids, ovarian, Shattuck's theory, 877
 sacrococcygeal, etiology of, 873
- Desmoid tumors, 655
 etiology, 657
 occurring in operative scars, 655
 surgical treatment, 659
- Development, anatomic errors in, 865
 cause and surgical significance, 865
- Device for holding solution bottles in operating rooms, 731
- Diabetes, Allen's treatment, 478
- Diabetics, diet after operation in, 479
 medical treatment, preparatory to surgical treatment, 476
- Diaphragmatic hernia, non-strangulated traumatic, 645
- Diet after operation in diabetics, 479
- Digestive tract, relation of spleen to, 529
- Diseases, general, infection as cause, 879
 nose and throat in etiology of, 593
 relation of tonsils to, 599
 local, infection as cause, 879
- Diverticulum, Meckel's etiology of, 878
- Divulsion of stricture of common bile-duct with forceps, 270
- Drainage in chronic empyema, 622
 in splenectomy, 547
 in subdiaphragmatic abscess, 307
 of gall-bladder, 261
- Ductless glands, 391
- Duodenal fistula, transperitoneal closure following nephrectomy, 349
 perforations, 293
 rupture, subphrenic abscess associated with, 305
 ulcer, bacteriology of, 58
 bulbar deformity as sign, 220
 chronic, 234
 chronic ulcer of stomach and, differentiation, 175
 closure of pylorus in operations for, 245
 complications of, 181
 diagnosis, 243
 essential factors in, 174
 etiology of, 240
 frequency of, 236
 heat in etiology of, 240
 hemorrhage in, 177, 180
 infection theory of cause, 240
 intermittency of, 244
 location of, 242
 pain in, 175, 176, 180
 perforation in, 242
 recurrence of symptoms after operation, 245
 situation of, 181
 stitch ulcer after operation for, 245
 symptoms of, 243
 treatment of, 244
 ulcer of stomach and, pyloric veins in differentiation, 241
 clinical syndromes, 185
 diagnosis, 198
 hemorrhage in, 189, 200
 notes on, 184
 pain in, 188, 190, 191, 192, 199, 206
 perforation in, 190
 symptoms of, 201

- Duodenal ulcer, regular type, 185**
 symptoms, 198
 ulcer of pyloric end of stomach
 and, differentiation, 212
 vomiting in, 189, 199
x-rays in diagnosis of, 200, 220
 value of history and clinical
 data in, 233
- Duodenum, cancer of, diagnosis, 198**
 diseases of, analysis of contents of
 stomach in diagnosis of, 195
 differential diagnosis, 194
 nausea in, 198
 pain in, 197, 198
 presence or absence of mucus in
 stomach as aid in diagnosis, 196
 tenderness in, 197
x-rays as aid in diagnosis, 196
 roentgen observation of gall-bladder
 and hepatic ducts after perforation
 into, 247
 union of common duct to, by rubber
 tube, 274
 direct, 272, 274
 two-row suture anastomosis,
 273
- Dyspepsia, qualitative food, 260**
 quantitative food, 260
- Dyspnea in malignant metastases in
 lungs, 611**
- EDEMA, angioneurotic, abdominal pain
 in, 825**
 visceral crises in, 823
- Emetin in pyorrhea, 21, 32**
- Empyema, chronic, Beck's paste in, 627**
 bismuth and vaselin in, 627
 decortication operation for, 632
 drainage in, 622
 Estlander's operation for, 630
 filling type of operation for, 634
 Fowler-Delorme operation for, 632
 localization of cavity in, 618
 muscle implantation operation for,
 634-644
 Ransohoff's operation for, 632
- Empyema, chronic, Schede's operation
 for, 631**
 sterilization of cavity in, 628
 surgical treatment, 628
 treatment of, 618
 localization of cavity, 618
 non-operative, 626
 surgical, 628
 without operation, 626
 vaccine treatment, 627
 Wilms' operation for, 629
- Endocarditis, relation of tonsils to, 597,
 600**
- Endothelioma, 926**
- Enlargement of spleen, 538**
- Entamoeba buccalis and Entamoeba
 histolytica, similarity between,
 30**
 in pyorrhea, 25, 29
 histolytica and Entamoeba buccalis,
 similarity between, 30
- Eosinophilia, splenomegaly with, path-
 ology of spleen in, 508**
 splenectomy in, 516
- Epidemic of appendicitis, 282**
 of parotitis, 282
- Epispadias, etiology of, 876**
- Epithelial cytoplasmia, migratory, 900,
 919**
 primary, 900, 907, 916, 919
 secondary, 900, 907, 917, 919
 tertiary, 900, 919
 vestiges, 888
- Epstein's method of determining per-
 centage of blood-sugar, 483**
- Erupting teeth, infection about, 20**
- Estlander's operation for chronic empy-
 ema, 630**
- Ether anesthesia, intratracheal, 715**
 indications, 715
 new apparatus and tube, 715
 technic of intubation, 718
 vaporizing apparatus, 721
- Evisceration and its supposed relation to
 sympathetic ophthalmia, 573**
- Ewald and Boas' test-breakfast, 98**
- Ewald's test-meal, 98**

- Excision of obstructed portion of common bile-duct, with end-to-end union, 268
- Exophthalmic goiter, 460
 operations for, results of, 463
 percentage of relapses, 462
 percentages of cured, 461
- Expectancy, life, goiter and, 456
- Experimental study of shock and hemorrhage, 739
- Extraperitoneal spaces, 298
- Extremities, 549
- Eye, evisceration of, supposed relation, to sympathetic ophthalmia, 573
- FAT necrosis of pancreas, 293, 294
- Faucial tonsils, 594
- Fibrocytoplasia, migratory, 917
 primary, 917
 secondary, 917
 tertiary, 917
- Fibrolipoma of larynx, 587
 diagnosis, 591
 etiology, 589
 treatment, 591
- Fibrosis, diffuse, of stomach, 135
- Filia terminalis, 872
- Filling type of operation in chronic empyema, 634
- Fillings, ill-fitting, infections about, 20
- Fistula, duodenal, transperitoneal closure, following nephrectomy, 349
 vesicovaginal, small, Amyx's operation for, 373
 • repair of, 373
- Follicular tonsillitis, recurring, 599
- Foreign bodies in bladder, 364
 swallowed by insane woman, 218
- Fowler-Delorme operation for chronic empyema, 632
- Fractures of nose, depressed, transplantation of cartilage for, 579
 technic of operation, 581
 shaft of humerus, ununited, transplantation of bone in, 669
- GALL-BLADDER, anatomy of, 258
 and hepatic ducts after perforation into duodenum, roentgen observation of, 247
 Bevan's incision for exposing, 267
 catarrhal, 250
 drainage of, 261
 in animals, 259
 inflammation of, causes, 251
 operations on, Bevan's incision for, 541
 subphrenic abscess associated with, 305
 papilloma of, 249
 perforations of, 294
 rupture of, subphrenic abscess associated with, 306
 strawberry, 250
 usefulness of, 259
- Gastric juice in production of ulcer of stomach, 72
- Gastroduodenal ulcer, bacteriology of, 58
- Gastro-enterostomy, development of ulcer in vicinity of, 156
 gastrojejunal ulcers after, 156
 jejunal ulcers after, 156
 retained suture material after, as cause of gastrojejunal ulcers, 172
- Gastrojejunal ulcers after gastro-enterostomy, 156
 retained suture material as cause, 172
 roentgenologic aspects, 156
 surgical aspects, 156
- Gaucher's disease, relation of spleen to, 535
 splenectomy in, 512, 535
- General papers, 737
- Germinative cells, 894
- Glands, ductless, 391
- Glossodermatitis tuberculo-fibrosa, 6
 tuberculo-ulcerosa, 6
- Glossopharyngeal nerve, injury of, in tonsillectomy, 56, 57
- Glycosuria, medical treatment, preparatory to surgical treatment, 476

- Glycosuria, transitory, 477
- Goiter and life expectancy, 456
- blood-pressure in, 448
 - cardiac lesions in, 443
 - clinical classification, 438
 - correlation of pathologic, clinical, and chemical data, tables showing, 426, 427, 430, 432
 - exophthalmic, 460
 - operations for, results of, 463
 - percentage of relapses, 462
 - percentages of cured, 461
 - heart lesions in, 443
 - hyperplastic, blood-pressure in, 452
 - non-hyperplastic, blood-pressure in, 452
 - pathologic changes in muscular system in, 438, 443
 - in nervous system in, 438, 445
 - relationships between clinical, pathologic, and chemical findings in, 422
- Gunshot wounds of abdomen, 292
- HAIR ball in stomach, 127
- Haudek's double-meal method of determining gastric motility, 106
- Head, 549
- Heart, Copenhagen, 857
- disease of, in syphilis, 846
 - blood-pressure, 850
 - physical findings, 848
 - symptoms, 847, 848
 - treatment, 851
 - lesions in goiter, 443
- Heat in etiology of chronic duodenal ulcer, 240
- in treatment of cancer of cervix, 378, 388
- Hematuria in non-surgical infection of kidneys and ureters, 337
- in ureteral calculus, 329
- Hemolytic anemia, pathology of spleen in, 506
- splenectomy in, 513
 - jaundice, pathology of spleen in, 507
 - relation of spleen to, 536
- Hemolytic jaundice, splenectomy in, 514, 536
- Hemorrhage and shock, experimental study, 739
- in chronic duodenal ulcer, 177, 180
 - ulcer of stomach, 177, 180
 - in duodenal ulcer, 189, 200
 - in ulcer of stomach, 189, 200, 204
 - internal, in abdomen, symptoms of, 356
- Henoch's purpura, 824
- Hepatic ducts and gall-bladder after perforation into duodenum, Roentgen observation of, 247
- injury to, restoration of bile-passage after, 264
- Hernia, diaphragmatic, non-strangulated traumatic, 645
- Herpes zoster, etiology, 779
- experimental production, 779
 - review of cases, 784
 - technic of, 783
 - historic review, 779
 - localization of streptococci from, 809
 - microscopic anatomy of lesions, 815
 - renal colic occurring with, 782
- Heuter's operation for bunion, 708
- Hour-glass stomach, treatment of, 217
- Hubb8he, 106, 115
- Humerus, ununited fractures of shaft, transplantation of bone in, 669
- Hydrocephalus, 551
- classification of, 552
 - etiology of, 553
 - treatment of, 556
- Hydroencephalocele, 552
- Hypermotility, gastric, in x-ray diagnosis of duodenal ulcer, 231
- Hypernephroma of kidney, 875
- Hyperperistalsis, gastric, in x-ray diagnosis of duodenal ulcer, 229, 232
- Hyperplasia, migratory, 894
- tertiary, 894
- Hyperplastic goiter, blood-pressure in, 452
- Hyperthyroidism, 460

- Hypertonus, gastric, in x-ray diagnosis of duodenal ulcer, 229
- Hypertrophic tonsillitis, chronic, 599
- Hypospadias, etiology of, 876
- Hysterectomy, abdominal, for cancer of uterus, 386
- vaginal, for cancer of uterus, 387
- ILL-FITTING crowns, bridges, and fillings, infections about, 20
- Incision, Bevan's, for operations on gall-bladder and biliary passages, 267, 541
- for exposure of kidney, 362
- for splenectomy, 541
- Infection about erupting teeth, 20
- about ill-fitting crowns, bridges, and fillings, 20
- as cause of local and general disease, 879
- local, bilateral parotid tumors due to, 47
- of mouth, 19
- treatment, 22
- of tonsil, recognition, 601, 602
- theory of cause of duodenal ulcer, 240
- Inflammation of gall-bladder, causes, 251
- Innervation in production of ulcer of stomach, 73
- Insane woman, foreign bodies swallowed by, 218
- Intraperitoneal space, 298
- left anterior, 299
- posterior, 299
- right anterior, 298
- posterior, 299
- Intratracheal ether anesthesia, 715
- indications, 715
- new apparatus and tube, 715
- technic of intubation, 718
- vaporizing apparatus, 721
- tube, 717
- Iodin, Alpha, 441
- compound in thyroid, 393, 422
- chemical nature, 393
- physiologic activity, 393
- JAUNDICE, hemolytic, pathology of spleen in, 507
- relation of spleen to, 536
- splenectomy in, 514, 536
- Jejunal ulcers after gastro-enterostomy, 156
- Judd's method of catching cystic duct and artery, 266
- KIDNEY, abscess of, as cause of perinephritic abscess, 313
- diseases of, diagnosis, significance of vesical symptoms, 320
- hypernephroma of, 875
- incision for exposure of, 362
- mesothelioma of, 875
- non-surgical infection, bacteriologic examination in, 340
- clinical review, 336
- cystitis in, 339
- cystoscopic examination, 338
- frequency of urination in, 337
- functional tests in, 339
- hematuria in, 337
- pain in, 337
- pyelogram in, 339
- treatment of, 341
- rupture of, as cause of perinephritic abscess, 314
- stone in, as cause of perinephritic abscess, 313
- diagnosis of, significance of vesical symptoms, 323
- tuberculosis of, as cause of perinephritic abscess, 312
- diagnosis, significance of vesical symptoms, 320
- nephrectomy for, management of ureter after, 361
- Knee-joint, injuries of, method of production, 684
- ligaments of, 681
- loose bodies in, effect of, 686
- indications for operation, 687
- method of production, 684
- operative technic, 692

- Knee-joint, loose bodies in, symptoms, 687
 mechanical derangements, 681
 method of production, 684
Kölliker's theory of specificity of tissues, 896
- LARYNGITIS**, relation of tonsils to, 599
Larynx, fibrolipoma of, 587
 diagnosis, 591
 etiology, 589
 treatment, 591
 lipoma of, 587
Lavage in non-surgical infection of kidneys and ureters, 342, 344
Leather-bottle stomach, 135
Leube's test-meal, 98
Leukemia, lymphatic, bilateral parotid tumors associated with, 42
 myelocytic, splenectomy in, 514
Life expectancy, goiter and, 456
Ligaments, crucial, 683
 of knee-joint, 681
 splenic, separation of, in splenectomy, 543
Ligation of common carotid for cirroid aneurysm, 565
 of splenic artery as preliminary step in splenectomy, 546
 of vascular pedicle in splenectomy, 544
 two-forceps method, with special reference to nephrectomy, 355
Lingual tonsil, 594
Lipoma of larynx, 587
 diagnosis, 591
 etiology, 589
 treatment, 591
Liver, cirrhosis of, relation of spleen to, 531
 splenectomy in, 514, 532
 relation of spleen to, 529
 syphilis of, 840
 treatment, 844
Loose bodies in knee-joint, effect of, 686
 indications for operation, 687
Loose bodies in knee-joint, method of production, 684
 operative technic, 692
 symptoms, 687
Lungs, cysts of, metastatic pulmonary malignancy and, x-rays in differentiation, 615
 metastatic malignancy in, cysts and, x-rays in differentiation, 615
 metastatic malignancy in, physical findings, 611
 radiographic diagnosis, 606
 symptoms, 611
 syphilis of lungs and, x-rays in differentiation, 614
 tuberculosis and, x-rays in differentiation, 614
 syphilis of, metastatic pulmonary malignancy and, x-rays in differentiation, 614
Lupus of tongue, 5, 6
 diagnosis, 8
Lymphatic leukemia, bilateral parotid tumors associated with, 42
Lymphatics of tonsils, 595
Lymphoid cells of tonsil, 595
Lymphoma, splenectomy in, 514
Lymphosarcoma, pathology of spleen in, 508
 splenectomy in, 514
- MACCARTY'S** classification of tumors, 898
Malignant metastases in lung, cysts and, x-rays in differentiation, 615
 physical findings, 611
 radiographic diagnosis, 606
 symptoms, 611
 syphilis of lung and, x-rays in differentiation, 614
 tuberculosis and, x-rays in differentiation, 614
 tumors of thyroid, 458
Mallet, operating, 793
Mastitis, chronic, cancer of breast and, relation between, 918

- Mastitis, chronic, trauma as etiologic factor, 920**
Mayo's (Charles H.) operation for bun-
 ion, 705
 after-care, 711
 technic, 710
 for varicose veins, 662
Meckel's diverticulum, etiology, 878
Mediastinum, disease of, in syphilis, 847
 blood-pressure, 850
 physical findings, 848
 treatment, 851
Melanoblastoma, 923
Melanocarcinoma, 923
Melanoepithelioma, 923
Melanoma, 923
Melanosarcoma, 923
Melanotic sarcoma, 923
Meningitis, relation of tonsils to, 600
Meningocele, 552, 872
 anterior, 871
Mesothelioma of kidney, 875
Metastases, malignant, in lungs, cysts
 and, x-rays in differentiation,
 615
 physical findings, 611
 radiographic diagnosis, 606
 symptoms, 611
 syphilis of lungs and, x-rays in
 differentiation, 614
 tuberculosis and, x-rays in differ-
 entiation, 614
Mikulicz's disease, 43
 treatment, 51
Motility of stomach, Haudek's double-
 meal method for determining,
 106
 roentgenologic determination, 96,
 100
 application of test, 112
 test-meals for determining, 98
Mouth, amebæ in, 25, 29
 infections of, 19
 treatment, 22
Mucus, presence or absence, in stomach,
 in diagnosis of diseases of stomach or
 duodenum, 196
Muscle implantation operation for
 chronic empyema, 634-644
Muscular rigidity in perforation of ab-
 domen, 295, 296
 system, pathologic changes in, in
 goiter, 438, 443
Myelocytic leukemia, splenectomy in,
 514
Myelomeningocele, 552
Myocarditis, relation of tonsils to, 600
- NAUSEA in diseases of duodenum, 198**
 of stomach, 198
Necropsy as public service, 937
 consent for, 940
 giving information to relatives, 943
 material, organized research on, 944
 need for, 938
Necrosis, fat, of pancreas, 293, 294
Neoplasms. See Tumors.
Neosalvarsan in syphilis, 841
Nephrectomy for tuberculosis, manage-
 ment of ureter after, 361
 procedures following, 349
 transperitoneal closure of duodenal
 fistulas following, 349
Nephritis, acute septic, perinephritic
 abscess and, differentiation, 318
 relation of tonsils to, 597, 600
Nephrolithiasis as cause of perinephritic
 abscess, 313
Nerve, glossopharyngeal, injury of, in
 tonsillectomy, 56, 57
Nervous system, pathologic changes in,
 in goiter, 438, 445
 syphilis of, treatment, 844
Neuralgia, diseased tonsil as cause,
 599
Neuritis, diseased tonsil as cause, 599
Neurosis of bladder, 323
Nose, fractures of, depressed, trans-
 plantation of cartilage
 for, 579
 technic of operation, 581
 in etiology of general diseases, 593

- OCHSNER's treatment of ulcer complicating varicose veins, 664
- Operating mallet, 733
- Ophthalmia, sympathetic, supposed relation of evisceration to, 573
- Osteomyelitis, relation of tonsils to, 600
- Ovarian dermoids, Shattuck's theory, 877
- PAIN**, abdominal, in angioneurotic edema, 825
- in abdomen, 197, 198
- in chronic duodenal ulcer, 175, 176, 180
- ulcer of stomach, 175, 176, 180
- in diseases of duodenum, 197, 198
- of stomach, 197, 198
- in duodenal ulcer, 188, 190, 191, 192, 199, 206
- in malignant metastases in lungs, 611
- in non-surgical infection of kidneys and ureters, 337
- in ulcer of stomach, 188, 190, 191, 192, 199, 200, 206
- localization of, in ureteral calculus, 327
- Palpation of ureteral calculus, 330
- Pancreas, fat necrosis of, 293, 294
- histologic changes in, after adrenalectomy, 486
- injuries to, in splenectomy, 544
- relation of adrenals to, 485
- Pancreatic juice, flow of, after adrenalectomy, 486
- Papers, general, 737
- Papilloma of gall-bladder, 240
- Parathyroids, injury of, at operation, 457
- Parotid tumors, bilateral, 37
- associated with lymphatic leukemia, 42
- diagnosis of, 49
- due to local infection, 47
- recurrent, 37
- syphilitic, 39
- treatment of, 50
- Parotid tumors, bilateral, tuberculous, 40
- Parotitis, epidemic of, 232
- Paste, Beck's, in chronic empyema, 627
- Pedicles, vascular, ligation of, two-forceps method, with special reference to nephrectomy, 355
- Percy's treatment of cancer of cervix, 378, 388
- Perforating ulcers of stomach and duodenum, symptoms, 201
- Perforation in abdomen, acute, 292
- muscular rigidity in, 295, 296
- necessity of immediate operation, 292, 294
- symptoms of, 295
- spontaneous, 292
- traumatic, 292
- in chronic duodenal ulcer, 242
- in duodenal ulcer, 190
- in ulcer of stomach, 190, 204
- of appendix, 294
- of bladder, 296
- of duodenum, 293
- of gall-bladder, 294
- of pancreas, 294
- of stomach, 294
- Pericarditis, relation of tonsils to, 600
- Perigastric abscess, 299
- Perinephritic abscess, 311
- acute septic nephritis and, differentiation, 318
- bacteriologic examination of urine in diagnosis of, 316
- classification of, 311
- cortical abscess as cause, 313
- diagnosis of, 316
- differential diagnosis, 318
- etiology, 312
- nephrolithiasis as cause, 313
- phenolsulphonephthalein test in diagnosis of, 317
- primary, 311
- pyelogram in diagnosis of, 317
- pyonephrosis as cause, 312
- renal, functional test in diagnosis of, 317

- Perinephritic abscess, renal, tuberculo-
 sis as cause, 312
 results after operation, 318
 rupture of kidney as cause, 314
 secondary, 311
 subdiaphragmatic abscess and, dif-
 ferentiation, 318
 traumatic perinephritis as cause, 31
 treatment, 318
 urinalysis in diagnosis of, 316
 without renal involvement, 315
 x-rays in diagnosis of, 317
 Perinephritis, traumatic, as cause of
 perinephritic abscess, 314
 Perisplenic abscess, 299
 Peritoneum, sensitiveness of, 296
 Peritonitis, subphrenic abscess associ-
 ated with, 301, 306
 Peritonsillar abscess, 599
 Pernicious anemia, pathology of spleen
 in, 504-506
 relation of spleen to, 537
 splenectomy in, 512, 537
 Pharyngitis, relation of tonsils to, 599
 Phenolsulphonephthalein test in diag-
 nosis of perinephritic abscess, 317
 Phlebitis, relation of tonsils to, 600
 Pleurisy, relation of tonsils to, 600
 Poisoning, snuff-, 854
 symptoms of, 857
 Polycytoplasia, 902
 Postmortem examination as public ser-
 vice, 937
 consent for, 940
 giving information to relatives,
 943
 need for, 938
 Postnatal hypothesis for origin of
 tumors, 888
 Pouch, Rathke's, 868
 Precancerous conditions, 904
 Prenatal hypothesis for origin of tumors,
 888
 Ptyalism in tuberculosis of tongue, 7
 Purpura, Henoch's, 824
 Pyelogram in diagnosis of perinephritic
 abscess, 317
 Pyelogram in non-surgical infection of
 kidneys and ureters, 339
 Pyelonephritis as cause of cystitis, 321
 diagnosis of, significance of vesical
 symptoms, 321
 Pyloric end of stomach, cancer of, ulcer
 and, differentiation, 209
 ulcer of, 209
 cancer and, differentiation, 209
 duodenal ulcer and, differ-
 entiation, 212
 Rodman's operation for, 212
 veins in differentiation of ulcer of
 stomach and duodenal ulcer, 241
 Pylorospasm as cause of gastric reten-
 tion, 115
 Pylorus, closure of, in operation for
 duodenal ulcer, 245
 Pyonephrosis as cause of perinephritic
 abscess, 312
 Pyorrhoea alveolaris, 20, 25
 emetin in, 21, 32
 Entamoeba buccalis in, 25, 29
 etiologic factors, 26
 relation of amebiasis to, 25
- QUINCY, 599**
- RACHISCHISIS, 552, 871
 Radium in Mikulicz's disease, 51
 Ransohoff's operation for chronic em-
 pyema, 632
 Rathke's pouch, 868
 Recurrent bilateral parotid tumors, 37
 Renal calculus as cause of perineph-
 ritic abscess, 313
 diagnosis, significance of vesical
 symptoms, 323
 colic occurring with herpes zoster,
 782
 Resection of obstructed portion of com-
 mon bile-duct, with end-to-end union,
 268
 Rests, adrenal, 888, 891
 Retractor, bladder, self-retaining, 734

Reverdin's operation for bunion, 709
 Rheumatism, tonsillitis and, relationship, 600
 Ribbert's hypothesis for origin of tumors, 887
 Riegel's test-dinner, 98, 99
 Boas and Strauss' modification, 99
 Riggs' disease. See *Pyorrhæa alveolaris*.
 Rodman's operation for ulcer of pyloric end of stomach, 212
 Röntgen rays. See *X-rays*.
 Rupture of duodenum, subphrenic abscess associated with, 305
 of gall-bladder, subphrenic abscess associated with, 306
 of kidney as cause of perinephritic abscess, 314

 SACROCOCCYGEAL dermoid tumors, etiology of, 873
 Salvarsan in syphilis, 840
 Sarcoma, alveolar, 926
 melanotic, 923
 of thyroid gland, 458
 Schede's operation for bunion, 708
 for chronic empyema, 631
 Sections of living tissue, unfixed, staining of, 722
 Semilunar cartilages, 683
 injuries of, indications for operation, 687
 method of production, 684
 symptoms, 687
 Sensitiveness of peritoneum, 296
 Septic splenomegaly, pathology of spleen in, 507
 splenectomy in, 514
 Shattuck's theory of ovarian dermoids, 877
 Shock and hemorrhage, experimental study, 739
 Snuff-poisoning, 854
 symptoms, 857
 Solution bottles, device for holding, in operating rooms, 731
 Spasm, vascular, 82

Spina bifida, 551, 872
 classification, 552
 etiology, 553
 occulta, 553
 club-foot in, treatment, 560
 operative treatment, 558
 treatment, 556
 Spleen, diseases of, 511
 enlargement of, 538
 pathology of, in abnormal conditions of blood, 500
 in acute febrile splenomegaly, 508
 in hemolytic anemia, 506
 jaundice, 507
 in lymphosarcoma, 508
 in pernicious anemia, 504-506
 in septic splenomegaly, 507
 in splenic anemia, 500-504
 in splenomegaly with eosinophilia, 508
 in syphilis with splenomegaly, 507
 studies in, 500
 relation of, to anemia, 529
 to blood, 533
 to cirrhosis of liver, 531
 to digestive tract, 529
 to Gaucher's disease, 535
 to hemolytic jaundice, 536
 to liver, 529
 to pernicious anemia, 537
 to splenic anemia, 535
 tuberculosis of, splenectomy in, 515
 wandering, splenectomy in, 515
 Splenectomy, adhesions in, 541
 after-care, 547
 Bevan's incision for, 541
 clinical notes on, 511
 closure of splenic space in, 546
 drainage in, 547
 in acute febrile splenomegaly, 515
 in adult form of splenic anemia in childhood, 518
 in anæmia pseudoleukæmica infantum, 522
 in cirrhosis of liver, 514, 532
 in Gaucher's disease, 512, 535
 in hemolytic anemia, 513

- Splenectomy in hemolytic jaundice, 514, 536
 in lymphoma, 514
 in lymphosarcoma, 514
 in myelocytic leukemia, 514
 in pernicious anemia, 512, 537
 in secondary infectious splenomegaly, 514
 in septic splenomegaly, 514
 in splenic anemia, 512, 535
 in childhood, 517
 of infancy, 522
 in splenomegaly with eosinophilia, 516
 in syphilis with splenomegaly, 514
 in tuberculosis of spleen, 515
 in von Jaksch's disease, 522
 in wandering spleen, 515
 incision for, 541
 injury to pancreas in, 544
 to stomach in, 545
 ligation of splenic artery as preliminary step in, 546
 of vascular pedicle in, 544
 mortality of, 547
 separation of splenic ligaments in, 543
 surgical considerations, 541
- Splenic anemia in childhood, adult form,
 splenectomy for, 518
 splenectomy for, 517
 in infancy, splenectomy for, 522
 pathology of spleen in, 500-504
 relation of spleen to, 535
 splenectomy in, 512, 535
 artery, ligation of, as preliminary step
 in splenectomy, 546
 ligaments, separation of, in splenectomy, 543
 space, closure of, in splenectomy, 546
- Splenomegaly, acute febrile, pathology
 of spleen in, 508
 splenectomy in, 515
 secondary infections, pathology of
 spleen in, 507
 splenectomy in, 514
 septic, pathology of spleen in, 507
- Splenomegaly, septic, splenectomy in,
 514
 syphilis with, pathology of spleen in,
 507
 splenectomy in, 514
 with eosinophilia, pathology of spleen
 in, 508
 splenectomy in, 516
- Staining sections of living tissue, un-
 fixed, 722
- Sterilization of cavity in chronic empy-
 ema, 628
- Stitch ulcers after operations for duo-
 denal ulcers, 245
- Stomach, body of, large ulcer of, 215
 cancer of, diagnosis, 201
 inoperability, evidences of, 138
 symptoms, 201
 x-rays in diagnosis of, 123, 202
 alteration of pyloric function,
 130
 altered motility, 132
 size and capacity of stomach,
 133
 carcinomatous ulcer, 137
 displacement of stomach, 134
 early cancer, 139
 filling defects, 125
 fungous type, 135
 gaping of pylorus, 131
 interpreting signs, 141
 latent cancer, 139
 lessened flexibility, 133
 mobility, 133
 mucoid type, 137
 operability, 137
 peristalsis, 131
 pyloric obstruction, 131
 scirrhus type, 136
 contents of, analysis, in diagnosis of
 diseases of stomach and duodenum,
 195
 diffuse fibrosis of, 135
 diseases of, analysis of contents of
 stomach in diagnosis of, 195
 differential diagnosis, 194
 nausea in, 198

Stomach, diseases of, pain in, 197, 198
 presence or absence of mucus in stomach as aid in diagnosis, 196
 tenderness in, 197
 x-rays as aid in diagnosis, 196
 hair ball in, 127
 hour-glass treatment of, 217
 hypermotility of, in x-ray diagnosis of duodenal ulcer, 231
 hyperperistalsis of, in x-ray diagnosis of duodenal ulcer, 229, 232
 hypertonus of, in x-ray diagnosis of duodenal ulcer, 229
 injury to, in splenectomy, 545
 leather-bottle, 135
 lesser curvature and antrum, ulcer of, 212
 motility of, Haudek's double-meal method for determining, 106
 roentgenologic determination, 96, 100
 application of test, 112
 test-meals for determining, 98
 mucus in, presence or absence, in diagnosis of diseases of stomach or duodenum, 196
 operation on, subdiaphragmatic abscess following, 306
 perforation of, 294
 posterior wall, ulcer of, 216
 pyloric end, cancer of, ulcer and, differentiation, 209
 ulcer of, 209
 cancer and, differentiation, 209
 duodenal ulcer and, differentiation, 212
 Rodman's operation for, 212
 syphilis of, diagnosis, 202
 treatment, 844
 trichobezoar in, 127
 ulcer of, 204
 bacteriology, 58
 Balfour's treatment, 213
 bile in production of, 94
 carcinomatous change in, 206
 cautery in treatment of, 213

Stomach, ulcer of, chronic, chronic duodenal ulcer and, differentiation, 175
 complications of, 181
 diagnosis of, essential factors in, 174
 duodenal ulcer and, pyloric veins in differentiation, 241
 hemorrhage in, 177, 180
 pain in, 175, 176, 180
 situation of, 181
 clinical syndromes, 185
 diagnosis, 198
 disturbed circulation in production of, 72
 following removal of adrenals, 87
 gastric juice in production of, 72
 hemorrhage in, 189, 200, 204
 innervation in production of, 73
 large, 215
 notes on, 184
 origin of, trophic element in, 70, 206
 pain in, 188, 190, 191, 192, 199, 200, 206
 pathogenesis, 276
 perforating, 190, 204
 subphrenic abscess associated with, 306
 symptoms of, 201
 symptoms, 198, 200
 trophic element in origin of, 70
 vomiting in, 189, 199
 x-rays in diagnosis of, 200
 water-trap, 103, 115
 Stomatodeum, 556
 Stratum germinativum, 908, 909
 Strauss and Boas' modification of Riegel's test-dinner, 99
 Strawberry gall-bladder, 250
 Streptococci, elective localization, 764
 technic of, 764
 in dairy products, epidemic of appendicitis and parotitis probably due to, 282
 localization of, from herpes zoster, 809
 Stricture of common bile-duct dilated with dilating forceps, 270

- Stricture of common bile-duct, excision of, with end-to-end union, 268
- Subdiaphragmatic abscess, 298
 associated with appendicitis, 303, 304
 with gall-bladder operations, 305
 with perforating gastric ulcers, 306
 with peritonitis, 301, 306
 with ruptured duodenum, 305
 gall-bladder, 306
 with tuberculous lesion elsewhere in abdomen, 307
 diagnosis, 304
 drainage in, 307
 duration, 304
 etiology of, 300
 following focal infection, 307
 operation on stomach, 306
 perinephritic abscess and, differentiation, 318
 prognosis, 308
 symptoms, 303
 treatment, 307
- Subhepatic pouch, 299
- Subphrenic abscess, 298. See also *Subdiaphragmatic abscess.*
 space, left extraperitoneal, 298
 right extraperitoneal, 298
- Surgical patients, after-care, 862
 care of, 859
 examination of, 859
 preparation of, 859
 shock, experimental study, 739
- Suture material, retained, after gastroenterostomy, as cause of gastrojejunal ulcers, 172
- Sympathetic ophthalmia, supposed relation of evisceration to, 573
- Syphilis, aneurysm of aorta in, blood-pressure, 850
 physical findings, 849
 symptoms, 847
 treatment, 851
 clinical prognosis, observations on, 836
 diagnosis, 837
- Syphilis, disease of aorta in, 846
 blood-pressure, 850
 physical findings, 849
 symptoms, 847, 848
 treatment, 851
 of heart in, 846
 blood-pressure, 850
 physical findings, 848
 symptoms, 847, 848
 treatment, 851
 of mediastinum in, blood-pressure, 850
 physical findings, 848
 symptoms, 847
 treatment, 851
 neosalvarsan in, 841
 of heart, symptoms, 847, 848
 of liver, 840
 treatment, 844
 of lungs, metastatic pulmonary malignancy and, x-rays in differentiation, 614
 of nervous system, treatment, 844
 of stomach, diagnosis, 202
 treatment, 844
 of tongue, tuberculosis of tongue and, differentiation, 8
 salvarsan in, 840
 treatment, 840
 Wassermann test in, 836
 with splenomegaly, pathology of spleen in, 507
 splenectomy in, 514
- Syphilitic aneurysm, symptoms, 847
 bilateral parotid tumors, 39
- Syngomyelocele, 553
- TALIPES, etiology of, 872
 Technic, 713
- Teeth, erupting, infection about, 20
- Temperature in malignant metastases in lungs, 611
- Tenderness in abdomen, 197
- Test, phenolsulphonephthalein, in diagnosis of perinephritic abscess, 317
 roentgen, for gastric motility, 96, 100

Test, roentgen, for gastric motility, application of, 112
 Wassermann, in syphilis, 836
 Test-breakfast, Ewald and Boas', 98
 Test-dinner, Riegel's, 98, 99
 Boas and Strauss' modification, 99
 Test-meal, Ewald's, 98
 Leube's, 98
 Test-meals for determining gastric motility, 98
 Throat in etiology of general diseases, 593
 Thyroid feeding in cretinism, 456
 gland, bacteria in, 457
 cancer of, 458
 chemical constituents, 395
 deficiency of, 456
 excessive activity, clinical aspects, 410
 infections of, 457
 iodine compound in, 393, 422
 chemical nature, 393
 physiologic activity, 393
 malignant tumors of, 458
 pathologic relationships, 438
 relationship of pathologic histology and iodine compounds of, 422
 sarcoma of, 458
 Thyrotoxicosis, 459
 blood-pressure and, 448
 Tibia, shaft of, non-regeneration, transplantation of bone for, 701
 Tissue, living, unfixed, staining sections of, 722
 Tissues, Kölliker's theory of specificity, 896
 Tongue, cold abscess of, 6
 lupus of, 5, 6
 diagnosis, 8
 syphilis of, tuberculosis of tongue and, differentiation, 8
 tuberculosis of, 3
 Bacillus tuberculosis in, 7
 clinical observations, summary of, 12
 diagnosis, 8
 frequency, 3

Tongue, tuberculosis of, histologic findings, 10, 12
 nodular form, 6
 papillomatous type, 7
 primary, 5
 prognosis, 9
 ptyalism in, 7
 routes of infection, 4
 sex frequency, 4
 symptoms, 7
 syphilis of tongue and, differentiation, 8
 treatment, 10
 ulcerative form, 6
 diagnosis, 9
 verrucose type, 7
 tuberculous ulcer of, 6
 cancerous ulcer and, differentiation, 9
 Tonsillar ring, Waldeyer's, 594
 Tonsillectomy, 52
 injury of glossopharyngeal nerve in, 56, 57
 technic of, 52
 Tonsillitis, chronic hypertrophic, 599
 follicular, recurring, 599
 Tonsils, bacteria in, 596
 faucial, 594
 in etiology of general diseases, 599
 infection of, recognition, 601, 602
 lingual, 594
 lymphatics of, 595
 lymphoid cells of, 595
 relation of, to arthritis, 597, 600
 to bronchitis, 599
 to cervical adenitis, 600
 to chorea, 600
 to endocarditis, 597, 600
 to laryngitis, 599
 to meningitis, 600
 to myocarditis, 600
 to nephritis, 597, 600
 to neuralgia, 599
 to neuritis, 599
 to osteomyelitis, 600
 to pericarditis, 600
 to pharyngitis, 599

- Tonsils, relation of, to phlebitis, 600
 to pleurisy, 600
 to rheumatism, 600
 removal of, 52
 surgery of, 52
 toxicity of, 596
 Toxicity of tonsils, 596
 Transitory glycosuria, 477
 Transperitoneal closure of duodenal fistulas following nephrectomy, 349
 Transplantation of bone for non-regeneration of tibial shaft, 701
 in ununited fractures of shaft of humerus, 669
 of cartilage for depressed fractures of nose, 579
 technic of operation, 581
 Trauma as etiologic factor in development of chronic mastitis and cancer, 920
 Traumatic diaphragmatic hernia, 645
 perforations in abdomen, 292
 perinephritis as cause of perinephritic abscess, 314
 Trichobezoar in stomach, 127
 Trocar, antrum, 585
 Trophic element in origin of ulcer of stomach, 70
 Trunk, 549
 Tuberculosis, bacillus of, in tuberculosis of tongue, 7
 metastatic pulmonary tuberculosis and, x-rays in differentiation, 614
 of kidney as cause of perinephritic abscess, 312
 diagnosis, significance of vesical symptoms, 320
 nephrectomy for, management of ureter after, 361
 of spleen, splenectomy in, 515
 of tongue, 3
 Bacillus tuberculosis in, 7
 clinical observations, summary of, 12
 diagnosis, 8
 frequency, 3
 histologic findings, 10, 12
 Tuberculosis of tongue, nodular form, 6
 papillomatous type, 7
 primary, 5
 prognosis, 9
 ptyalism in, 7
 routes of infection, 4
 sex frequency, 4
 symptoms, 7
 syphilis of tongue and, differentiation, 8
 treatment, 10
 ulcerative form, 6
 diagnosis, 9
 verrucose type, 7
 Tuberculous bilateral parotid tumors, 40
 ulcer of tongue, 6
 cancerous ulcer and, differentiation, 9
 Tumors, arterial, cirroid, 561
 bilateral parotid, 37
 associated with lymphatic leukemia, 42
 diagnosis of, 49
 due to local infection, 47
 recurrent, 37
 syphilitic, 39
 treatment of, 50
 tuberculous, 40
 symmetry, 891
 classification of, 898
 dermoid, sacrococcygeal type, etiology of, 873
 desmoid, 655
 etiology of, 657
 occurring in operative scars, 655
 surgical treatment, 659
 MacCarty's classification, 898
 malignant, of thyroid, 458
 of stump of cystic duct after cholecystectomy, 267
 origin of, Cohnheim's hypothesis, 886
 postnatal hypothesis, 888
 prenatal hypothesis, 888
 Ribbert's hypothesis, 887
 Two-forceps method for ligation of vascular pedicles, with special reference to nephrectomy, 355

- ULCER, cancerous, of tongue, tuberculous ulcer of tongue and, differentiation, 9
 complicating varicose veins, 661
 Ochsner's treatment, 664
 duodenal, bacteriology of, 58
 bulbar deformity as sign, 220
 chronic, 234
 chronic ulcer of stomach and, differentiation, 175
 closure of pylorus in operations for, 245
 complications of, 181
 diagnosis of, 243
 essential factors in, 174
 etiology of, 240
 frequency of, 236
 heat in etiology of, 240
 hemorrhage in, 177, 180
 infection theory of cause, 240
 intermittency of, 244
 location of, 242
 pain in, 175, 176, 180
 perforation in, 242
 recurrence of symptoms after operation, 245
 situation of, 181
 stitch ulcer after operation for, 245
 symptoms of, 243
 treatment of, 244
 ulcer of stomach and, pyloric veins in differentiation, 241
 clinical syndromes, 185
 diagnosis of, 198
 hemorrhage in, 189, 200
 notes on, 184
 pain in, 188, 190, 191, 192, 199, 206
 perforation in, 190
 symptoms of, 201
 regular type, 185
 symptoms of, 198
 ulcer of pyloric end of stomach and, differentiation, 212
 vomiting in, 189, 199
 x-rays in diagnosis of, 200, 220
- Ulcer, duodenal, x-rays in diagnosis of, value of history and clinical data in, 233
 gastroduodenal, bacteriology of, 58
 gastrojejunal, after gastro-enterostomy, 156
 retained suture material as cause, 172
 roentgenologic aspects, 156
 surgical aspects, 156
 jejunal, after gastro-enterostomy, 156
 of lesser curvature and antrum of stomach, 212
 of posterior wall of stomach, 216
 of pyloric end of stomach, 209
 cancer and, differentiation, 209
 duodenal ulcer and, differentiation, 212
 Rodman's operation for, 212
 of stomach, 204
 bacteriology, 58
 Balfour's treatment, 213
 bile in production of, 94
 carcinomatous change in, 206
 cautery in treatment of, 213
 chronic, chronic duodenal ulcer and, differentiation, 175
 complications of, 181
 diagnosis of, essential factors in, 174
 duodenal ulcer and, pyloric veins in differentiation, 241
 hemorrhage in, 177, 180
 pain in, 175, 176, 180
 situation of, 181
 clinical syndromes, 185
 diagnosis, 198
 disturbed circulation in production of, 72
 following removal of adrenals, 87
 gastric juice in production of, 72
 hemorrhage in, 189, 200, 204
 innervation in production of, 73
 large, 215
 notes on, 184
 origin of, trophic element in, 70

- Ulcer of stomach, pain in, 188, 190, 191, 192, 199, 200, 206
 pathogenesis of, 276
 perforating, subphrenic abscess associated with, 306
 perforation in, 190, 204
 symptoms of, 201
 symptoms, 198, 200
 trophic element in origin of, 70
 vomiting in, 189, 199
 x-rays in diagnosis of, 200
 stitch, after operations for duodenal ulcer, 245
 tuberculous, of tongue, 6
 cancerous ulcer and, differentiation, 9
- Ureteral calculus, 327
 diagnosis, sources of error, 332
 hematuria in, 329
 localization, 333
 occurrence, 335
 pain in, localization of, 327
 palpation of, 330
 sources of error in diagnosis, 332
 treatment, 331
 urinalysis in, 329
 vesical irritability in, 329
 x-rays in diagnosis, 332
- Ureters, management of, after nephrectomy for tuberculosis, 361
 non-surgical infection, bacteriologic examination in, 340
 clinical review, 336
 cystitis in, 339
 cystoscopic examination, 338
 frequency of urination in, 337
 functional tests in, 339
 hematuria in, 337
 pain in, 337
 pyelogram in, 339
 treatment of, 341
- Urinalysis in diagnosis of perinephritic abscess, 316
 in ureteral calculus, 329
- Urination, frequency of, in non-surgical infection of kidneys and ureters, 337
- Urine, bacteriologic examination of, in diagnosis of perinephritic abscess, 316
- Urogenital organs, 309
- Uterus, cancer of, abdominal hysterectomy for, 386
 inoperable, treatment of, 389
 operations for, relative merits, 385
 vaginal hysterectomy for, 387
 Wertheim's operation for, 386
- VACCINE treatment of chronic empyema, 627
- Vaccines in non-surgical infection of kidneys and ureters, 341, 342, 343
- Vaginal hysterectomy for cancer of uterus, 387
- Varicose veins, 660
 etiology, 660
 Mayo's (C. H.) operation for, 662
 operative treatment, 662
 post-operative treatment, 668
 preoperative treatment, 662
 selection of cases for operation, 661
 skin in, 661
 ulcer complicating, 661
 Ochsner's treatment, 664
- Vascular pedicles, ligation of, two-forceps method, with special reference to nephrectomy, 355
 spasm, 82
- Veins, pyloric, in differentiation of ulcer of stomach and duodenal ulcer, 241
 varicose, 660
 etiology of, 660
 Mayo's (C. H.) operation for, 662
 operative treatment, 662
 post-operative treatment, 668
 preoperative treatment, 662
 selection of cases for operation, 661
 skin in, 661
 ulcer complicating, 661
 Ochsner's treatment, 664
- Vermiform appendix, perforation of, 294
- Vesical irritability in ureteral calculus, 329

Vesical symptoms as result of extra-vesical cause, 324
 inflammatory extension as cause, 325
 malignant involvement as cause, 325
 mechanical obstruction to urinary flow as cause, 325
 pressure of tumor as cause, 324
 significance of, in diagnosis of pyelonephritis, 321
 of renal calculus, 323
 conditions, 320
 tuberculosis, 320
 Vesicovaginal fistula, small, Amyx's operation for, 373
 repair of, 373
 Visceral crises in angioneurotic edema, 823
 Vomiting in duodenal ulcer, 189, 199
 in ulcer of stomach, 189, 199
 Von Jaksch's disease, splenectomy in, 522

 WALDEYER's tonsillar ring, 594
 Wandering spleen, splenectomy in, 515
 Wassermann test in syphilis, 836
 Water-trap stomach, 103, 115
 Weight, loss of, in malignant metastasis in lungs, 611
 Wertheim's operations for cancer of uterus, 386
 Wilms' operation for chronic empyema, 629
 Wolff-Gärtner ducts, 888
 Wounds, gunshot, of abdomen, 292
 Wyeth's treatment of cirroid aneurysm, 564

X-RAY determination of gastric motility, 96, 100
 application of test, 112
 examination of gall-bladder and hepatic ducts after perforation into duodenum, 247
 in diagnosis of cancer of stomach, 123, 202
 alteration of pyloric function, 130
 altered motility, 132
 size and capacity of stomach, 133
 carcinomatous ulcer, 137
 displacement of stomach, 134
 early cancer, 139
 filling defects, 125
 fungous type, 135
 gaping of pylorus, 131
 interpreting signs, 141
 latent cancer, 139
 lessened flexibility, 133
 mobility, 133
 mucoid type, 137
 operability, 137
 peristalsis, 131
 pyloric obstruction, 131
 scirrhus type, 136
 of diseases of duodenum, 196
 of stomach, 196
 of duodenal ulcer, 200, 220
 value of history and clinical data in, 233
 of gastrojejunal ulcers, 156
 of metastatic malignancy in lungs, 606
 of perinephritic abscess, 317
 of ulcer of stomach, 200
 of ureteral calculus, 332
 in Mikulicz's disease, 51

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